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Contents on Inside Cover

American Heart Journal

CONTENTS FOR NOVEMBER, 1953

Original Communications

	Page
Mitral Stenosis and Cor Pulmonale. Alberto C. Taquini, M.D., Bernardo B. Lozada, M.D., Reinaldo J. Donaldson, M.D., Robinson E. H. D'Aiutolo, M.D., and Enrique S. Ballina, M.D., Buenos Aires, Argentina	639
Congenital Anomalies of the Mitral Valve. John T. Prior, M.D., Syracuse, N. Y.	649
Anatomic Variations in the Tetralogy of Fallot. Thomas G. Baffes, M.D., Frank R. Johnson, M.D., Willis J. Potts, M.D., and Stanley Gibson, M.D., Chicago, Ill.	657
The Electrocardiogram in Congenital Heart Disease and Mitral Stenosis. Richard S. Cosby, M.D., David C. Levinson, M.D., Sim P. Dimitroff, M.D., Robert W. Oblath, M.D., Lawrence M. Herman, M.D., and George C. Griffith, M.D., Los Angeles, Calif.	670
Spread of Activation in the Left Ventricular Wall of the Dog. I. D. Durrer, M.D., and L. H. van der Tweel, M.S., Amsterdam, Holland	683
Comparison of the Displacement, Velocity, and Acceleration Ballistocardiograph in Coronary Heart Disease. J. E. Smith, M.D., Washington, D.C.	692
Ballistocardiography With Elimination of the Influence of the Vibration Properties of the Body. Wolf-Wito von Wittern, Dayton, Ohio	705
Flow Through Collapsible Tubes. Simon Rodbard, M.D., Ph.D., and Hiroshi Saiki, B.S., Chicago, Ill.	715
Functional Cardiovascular Disturbances—Their Response to Drugs Acting on the Autonomic Nervous System. Gustav Schimert, M.D., Munich, Germany	726
Ventricular Fibrillation Elicited by Focal Cooling. D. Scherf, M.D., S. Blumenfeld, M.D., and R. Terranova, M.D., New York, N. Y.	741
Preliminary Observations of Rauwiloid-Hexamethonium Combined Therapy of Hypertension. Ralph V. Ford, M.D., and John H. Moyer, M.D., Houston, Texas	754
Echinococcosis of the Heart. Amal K. Kurban, M.D., Adnan I. Shafik, M.D., Safouh A. Attar, M.D., and Gregory A. Dragatsi, M.D., D.T.M. and H., Beirut, Lebanon	764

Clinical Reports

Rheumatic Heart Disease in Dextrocardia With Complete Situs Inversus. John M. Bleyer, M.D., and William Saphir, M.D., Chicago, Ill.	772
Functional Cor Triloculare. Freeman L. Rawson, Jr., M.D., and Alexander A. Doerner, M.D., Staten Island, N. Y.	779

Review of Meeting

Fourth Inter-American Congress of Cardiology, Buenos Aires, Argentina, 1952. Part II. Pedro Cossio, M.D., and Hector Caul, M.D., Buenos Aires, Argentina	784

Announcement

Announcement	797

Book Review

Book Review	798

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American Heart Journal

VOL. 46 NOVEMBER, 1953 NO. 5

Original Communications

MITRAL STENOSIS AND COR PULMONALE

ALBERTO C. TAQUINI, M.D., BERNARDO B. LOZADA, M.D., REINALDO J. DONALDSON, M.D., ROBINSON E. H. D'AIUTOLO, M.D., AND ENRIQUE S. BALLINA, M.D.

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AMONG patients with mitral stenosis few are outstanding for the fact that they follow a rapidly downhill course, with early development of signs of right ventricular strain and congestive heart failure.

The clinical behavior of these patients is consistently uniform and is characterized mainly by the predominance of respiratory symptoms and the appearance of clear-cut evidence, both radiologic and electrocardiographic, of right ventricular hypertrophy. The manner in which this right-sided heart strain appears, in many aspects similar to that of cor pulmonale, has led us to suspect that its presence in patients with mitral stenosis could be the result of an increased resistance in the pulmonary circulation consequent to changes in the pulmonary vascular tree and in the lungs, and in part, at least, independent of the resistance represented by the narrowing of the mitral valve.[1-4] With this in mind these patients have been grouped together under the heading of "mitral stenosis with cor pulmonale".

Many of these cases present frank clinical evidence of pulmonary participation, which coupled with the post-mortem findings has led us to believe that these vascular changes are not solely due to the pulmonary engorgement and hypertension present in cases of this nature but that they are partly the result of interstitial and/or vascular changes in the lungs, perhaps some of them of the same rheumatic etiology as the heart disease itself.[5]

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Received for publication June 8, 1953.

Others have argued that these pulmonary vascular changes form a protective mechanism, in the sense that they serve to protect the pulmonary capillaries from increases in cardiac output too large to by-pass the stenotic mitral valve without great increases in pulmonary capillary pressure.[6] It is our impression that this interpretation, though true in some ways, can lead to an erroneous evaluation from a clinical point of view. In fact, it seems that from the time such protective mechanism appears these patients continue rapidly downhill.

Since this rapid evolution can be checked by surgery, should this treatment be applied at the opportune moment, we have deemed it of interest to present in this report data on the clinical and functional behavior of a group of patients with mitral stenosis of this particular type.

MATERIAL

This study comprises a group of thirty patients which we considered to present satisfactory evidence of belonging to this clinical entity, selected by the diagnostic criteria to be established. Of these thirty, eighteen were considered to have pure mitral stenosis, seven had both mitral stenosis and regurgitation, four had combined mitral, aortic, and tricuspid involvement, and the remaining case was complicated by severe arterial hypertension.

According to the nature of their valvular involvement, these cases have been grouped as follows: (1) pure mitral stenosis; (2) mitral stenosis plus regurgitation; (3) combined mitral, aortic, and tricuspid lesions.

METHODS

All cases had complete clinical histories, including radiologic and electrocardiographic examination, and routine laboratory tests. Venous pressure and circulation time were obtained in all hospitalized patients, and those that died during their hospital stay were studied postmortem.

The following diagnostic criteria were adopted for the selection of these cases: (1) a history of a severe respiratory distress, with paroxysms of asthmatic-like breathing and frequent hemoptyses; (2) very pronounced dyspnea on effort, rapidly progressive; (3) radiologic evidence of right ventricular enlargement with markedly dilated pulmonary arteries, usually with surprisingly little evidence of left atrial enlargement; (4) typical electrocardiographic signs of right ventricular hypertrophy; and (5) a rapidly downhill course with early appearance of congestive heart failure.

In those patients in whom physiologic studies were carried out, these consisted of cardiac catheterization and its accessory techniques, with determination of cardiac output and pulmonary pressures at rest and during exercise. The details of the techniques used in this study are presented in a previous report.[7]

RESULTS

Frequency.—Of these thirty cases, twenty-four were selected from a total of 630 patients with rheumatic heart disease studied at the Centro de Investigaciones Cardiológicas, corresponding to 3.8 per cent of the total.

This percentage changes considerably if the proportion of cases with cor pulmonale is analyzed in each separate group, as seen in Table I.

TABLE I. INCIDENCE OF COR PULMONALE IN TYPES OF RHEUMATIC HEART DISEASE

DIAGNOSIS	NUMBER OF CASES	COR PULMONALE	PER CENT
R.H.D.	630	24	3.8
Pure mitral stenosis	77	17	22.08
Mitral stenosis plus regurgitation	163	5	3.07
Combined mitral aortic and tricuspid lesions	37	2	5.4
Mitral and aortic lesions only	143	0	0
Aortic lesions only	40	0	0

It is to be noted that this clinical pattern was not seen in such forms as mitral and aortic valve lesions or in lesions affecting the aortic valve only.

Symptoms.—These are summarized in Table II.

Dyspnea: Dyspnea on effort was pronounced in all eighteen cases with pure mitral stenosis, in five of the seven with stenosis plus regurgitation, and in three of the four with mitral and tricuspid lesions. Paroxysmal dyspnea was present in six patients with pure stenosis and in two with mitral stenosis and regurgitation.

Antecedent bronchitis, usually severe, with asthmatic-like breathing as evidenced by wheezing, with persistent cough, was present in sixteen of the eighteen cases with pure mitral stenosis; in five of the patients with stenosis

TABLE II

	MITRAL STENOSIS (18 CASES)	DOUBLE MITRAL LESION (7 CASES)	MITRAL AND TRICUSPID LESIONS (4 CASES)	DOUBLE MITRAL LESION AND HYPERTENSION (1 CASE)
Severe dyspnea	18	5	3	0
Moderate dyspnea	0	2	1	1
Paroxysmal dyspnea	6	2	0	0
Bronchitis	16	5	3	1
Venous stasis	8	4	3	0
Edema	8	4	3	0
Sinus rhythm	11	5	2	1
Auricular fibrillation	7	2	2	0
Right ventricular strain	18	7	4	1
Radiological signs	18	7	4	1

and regurgitation; in three of the four with associated tricuspid lesions; and also in the patient complicated by severe hypertension.

Edema and venous pressure: Edema of the lower extremities, accompanied by elevated venous pressure, was present in eight patients belonging to the first group, in four of the second, and in three of the four corresponding to group three, with associated mitral and tricuspid lesions.

Electrocardiogram: Typical tracings of these patients are seen in Fig. 1. The rhythm was found to be normal sinus in eleven of the eighteen cases forming Group 1, in five of the seven belonging to Group 2, in two of the four in Group 3, and in the patient with associated severe hypertension. The remaining cases of all groups had auricular fibrillation. Thus 65 per cent of the total had normal sinus rhythm, and 35 per cent had auricular fibrillation.

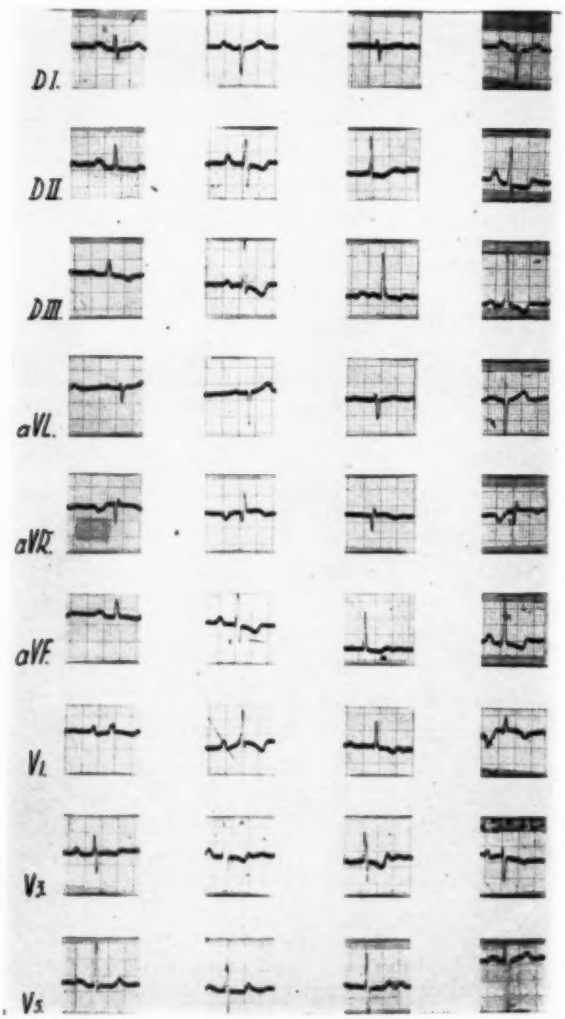

Fig. 1.—Electrocardiograms showing right ventricular hypertrophy.

Auriculoventricular conduction time was normal in all cases with sinus rhythm. The ventricular complexes showed typical signs of right ventricular hypertrophy in all these cases. In some, the gradual appearance of this pattern could be followed over a period of years, as in patient G.R.M., in whom it disappeared after commissurotomy (Fig. 2).

Roentgenogram: Cardiac enlargement, due mainly to dilatation of the right ventricle, with marked dilatation of the pulmonary artery and its main branches and with increased bronchovascular markings and clear lung fields, constituted the characteristic roentgenographic appearance of these cases. Attention is drawn to the fact that left atrial enlargement was not considerable in these patients,

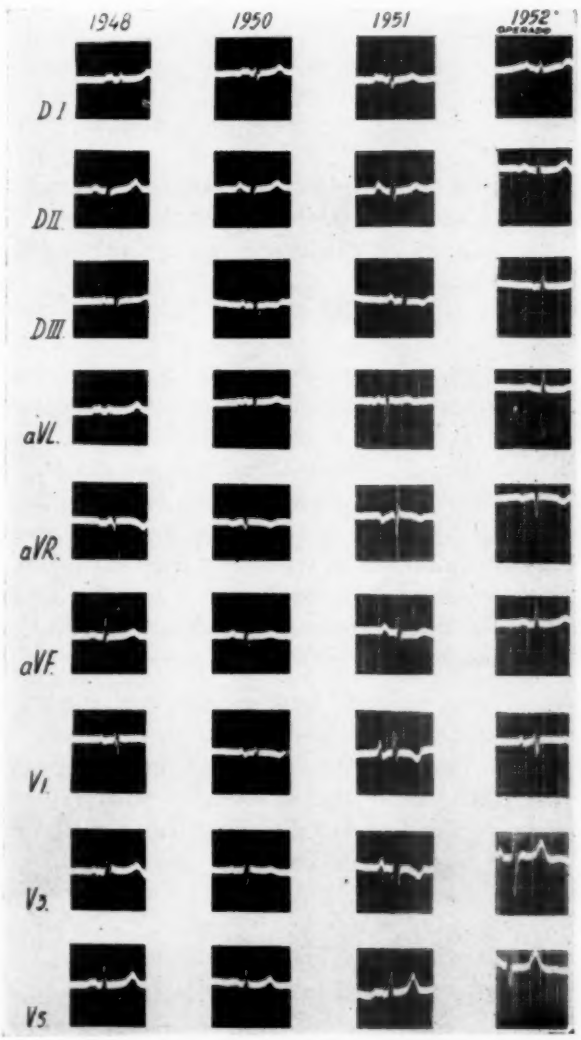

Fig. 2.—Serial electrocardiograms of patient 7398 in which can be seen the progression of the right ventricular hypertrophy and its disappearance one year after mitral commissurotomy.

TABLE III. PHYSIOLOGIC DATA IN PATIENT

PATIENT	AGE SEX	BODY SURFACE AREA (M^2)	ARTERIAL OXYGEN SATURATION (%)		OXYGEN CONSUMPTION C.C./MIN./M^2		A_1V_1 OXYGEN DIFFERENCE (C.C./LT.)		CARDIAC INDEX (LT./MIN./M^2)	
			REST	EXER.	REST	EXER.	REST	EXER.	REST	EXER.
M.L.Z.	38 F	1.40	91.0	94.0	155	345	58.2	118.0	2.67	3.09
I.F.	41 M	1.68	91.0	97.0	168	286	69.7	112.0	2.41	2.58
E.T.V.	39 M	1.58	92.5	—	161	—	82.0	—	1.97	—
A.S.L.	37 F	1.44	—	—	194	264	—	—	—	—

a finding that contrasted with the rest of the radiologic examination. Figure 3 illustrates the radiologic changes characteristic of these cases. Figure 4 was obtained during an acute attack of rheumatic pneumonitis proved by necropsy.

Functional Studies.—The data pertaining to these cases are presented in Table III.

The circulatory dynamics at rest show that these cases had extremely low cardiac indices, with correspondingly high auriculoventricular oxygen differences. The pulmonary capillary pressure was very high in two of the three cases in which it was determined, and the pulmonary arterial mean pressure was noticeably elevated in all four cases standing out clearly from the other group of cases that have been studied.[7] The pressure gradient between the pulmonary arterial and capillary pressure was found to be extremely high in all three cases in which these two pressures were recorded, giving rise to a greatly increased pulmonary arteriolar resistance. The total pulmonary resistance and the work of the right ventricle were also extremely elevated in these cases.

These changes, present at rest, were exaggerated during exercise. As a rule, the cardiac index of these patients, low at rest, showed no proportionate increase during exercise. The pulmonary artery mean pressure, already markedly elevated at rest, rose considerably during exercise, with values between 90 and 100 mm. Hg in all four cases. The right ventricular work calculated against pressure shows in these cases the most extreme vaues.

DISCUSSION

It has been seen that this type of clinical pattern occurs more frequently in cases in which the valvular involvement is predominantly stenosis of the mitral valve, its incidence being 22 per cent in these cases as compared to 3.8 per cent for all cases of rheumatic heart disease.

WITH MITRAL STENOSIS AND COR PULMONALE

PULMONARY ARTERIAL PRESSURE (MM. HG)				PULMONARY CAPILLARY MEAN PRESSURE (MM. HG)	MEAN PRESSURE GRADIENT (MM. HG)	PULMONARY ARTERIOLAR RESISTANCE (DYNES/SEC. CM.$^{-5}$)	TOTAL PULMONARY RESISTANCE (DYNES/SEC. CM.$^{-5}$)		RIGHT VENTRICULAR WORK KG./MIN./M^2	
REST		EXERCISE								
S/D	M	S/D	M	REST	REST	REST	REST	EXER.	REST	EXER.
103/53	78	115/75	92	—	—	—	1670	1970	2.84	4.00
100/50	70	125/75	100	25	45	890	1380	1850	2.30	3.51
82/58	65	97/70	85	35	30	848	1750	—	1.82	—
105/65	78	130/75	95	38	40	—	—	—	—	—

The significance of these figures assumes considerable importance at this time, because of the recent interest in operative attacks upon the stenosed mitral valve. It is, therefore, important to identify this type of case in the preoperative evaluation of patients with mitral stenosis, as we feel that the pulmonary changes which characterize these cases may be reversible when arrested at the initial stages of their development but are most probably unchangeable when far advanced. The surgical implications of this are easily understood. So far, the results obtained in the surgical treatment of our cases, to be reported later, show that the evolution of these patients can be stopped if attacked at the proper time. For these reasons the clinical differentation of these patients should be attempted in all cases of mitral stenosis. In this respect it has been shown that they are characterized by a particular clinical and physiologic pattern, not seen in other cases.

The dyspnea observed in these patients is especially pronounced in all its forms. The presence of the tight mitral stenosis partly explains the dyspnea characteristic of these cases. However, the pulmonary disorder must also be kept in mind. In this respect an important factor is the pulmonary interstitial fibrosis which reduces the elasticity of the lungs, causing a reduction of the maximum breathing capacity and a lowering of the threshold for dyspnea. It should also be borne in mind that these cases have a tendency to bronchiolar spasm, very likely a particular type of reaction to the stimuli represented by pulmonary involvement.

The early appearance of congestive heart failure is characteristic of this type of patient. This is a consequence of the extreme degree of pulmonary hypertension found in these cases, which constitutes a severe burden for the right ventricle, already overtaxed initially by the valvular lesion itself, but which alone is seldom responsible for the right ventricular incompetence.

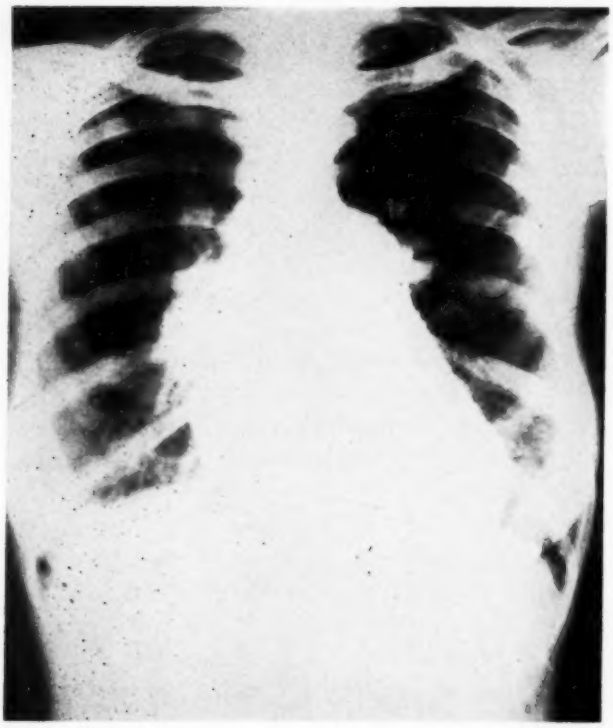

Fig. 3.—Teleroentgenogram showing the marked enlargement of the right ventricle and the dilatation of the pulmonary artery and its main branches.

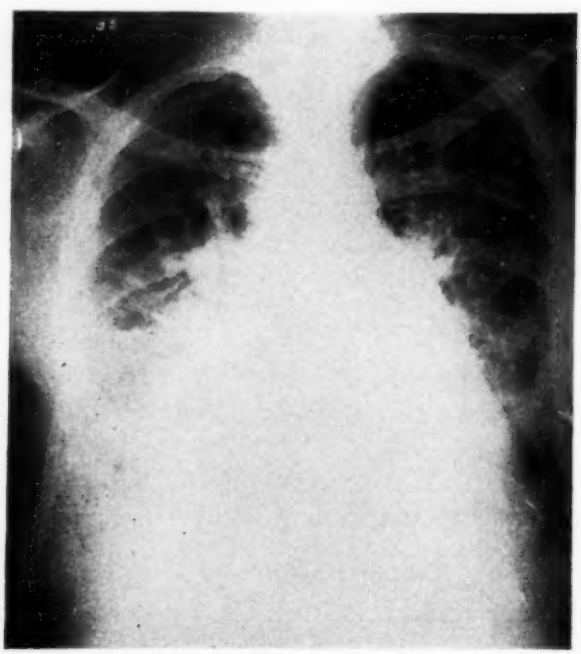

Fig. 4.—Teleroentgenogram showing characteristic cardiovascular changes and also evidence of pulmonary disease. Post-morten examination showed rheumatic involvement of the lungs.

The presence of a functional tricuspid insufficiency is rather common. When it is present, it usually disappears after operation. The same thing happens with the diastolic murmur due to pulmonary incompetence, which is frequently found in these patients.

Occasionally the appearance of acute episodes of right-sided heart failure, with signs of functional tricuspid insufficiency, are brought on by intercurrent pulmonary infections, similar to what we have called "bronchogenic subacute cor pulmonale".[8] This type of failure is usually reversible, being influenced mainly by appropriate therapy directed towards the bronchopulmonary disorder.

From the electrocardographic point of view, these patients are characterized by the constant finding of the pattern of right ventricular hypertrophy. This is in keeping with studies that have shown the correlation between electrocardiographic evidence of right ventricular hypertrophy and the pulmonary arterial pressure.[9-11] Another interesting electrocardiographic finding is the fact that the great majority of these patients have normal sinus rhythm, which would appear to point to the fact that the left atrium is not particularly affected in these patients. The latter statement is further corroborated by radiologic examination, which showed that the left auricular enlargement was not proportional to that of the right ventricle.

From a functional point of view the behavior of these patients also shows a rather definite pattern, characterized mainly by extremely high pressure in the pulmonary circuit, with a marked increase in the pulmonary arteriolar resistance. The cardiac output tends to be low and shows no corresponding increase during exercise, in spite of the great rise in pressures.

SUMMARY

Careful evaluation of patients with mitral stenosis has led the authors to differentiate a special type, to which the name of "mitral stenosis and cor pulmonale" has been given and which is characterized by the following points: (1) a history of pronounced respiratory symptoms; (2) an extreme degree of dyspnea; (3) electrocardiographic and roentgenographic evidence of marked right ventricular hypertrophy; (4) the early appearance of congestive heart failure; (5) marked alterations in circulatory dynamics with extremely high pressures n the pulmonary circulation.

The pathogenesis of this "mitral stenosis and cor pulmonale" is marked by severe changes in the small pulmonary vessels of these patients. The clinical and physiologic differentiation of these patients is stressed.

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CONGENITAL ANOMALIES OF THE MITRAL VALVE

Two Cases Associated With Long Survival

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CONGENITAL defects of the mitral valve are considered to be a rare variety of cardiac anomaly, the more severe degrees of which are seldom compatible with life beyond the neonatal period. Patten[1] states that not uncommonly the semilunar valves of the aorta or the pulmonary artery may show two cusps or four, instead of the usual three. Similarly, Patten adds that there may be irregularities in the configuration of the flaps of the atrioventricular valves or the manner in which they are stayed by tendinous cords and papillary muscles. If the valves adequately close the orifices which they guard, such anomalies are not likely to be of serious functional importance. Stenosis[2] and atresia[3] appear to be the most commonly reported congenital defects of the mitral orifice, each occurring with a variety of associated anomalies including endocardial fibro-elastosis.[4] Infants with these anomalies are either stillborn or survive only a very short period during which evidence of cardiac embarrassment is manifest.

It is the purpose of this report to present two unusual abnormalities of the mitral valve and its appendages. The first case, in which there was marked dysplasia of the chordae tendineae of the posterior leaflet of the mitral valve, survived with no cardiac embarrassment until the age of twenty-six. There were other cardiac and extracardiac congenital abnormalities found at necropsy in this patient. The second case fits into the group known as "double mitral orifice"[5] or "duplication of the mitral valve,"[6] although this patient actually had three mitral openings rather than the usually encountered double orifice. This anomaly was undoubtedly an "incidental finding" since the individual died at the age of seventy-two primarily of heart failure as a result of calcific aortic stenosis.

CASE REPORTS

Case 1.—P.G., a 26-year-old white male engineer was admitted to Syracuse Memorial Hospital Feb. 19, 1952, complaining of marked shortness of breath of two days' duration. Six years previously, upon entry into the Navy, he had been told he had a heart murmur. At the time of separation from the Navy two years later, the examining medical officer again mentioned the murmur but told him it was not serious. Nine months later the patient underwent a routine Navy follow-up examination and was told that the murmur was of sufficient severity to disqualify him for continued service. He consulted his private physician and arrangements were made for

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cardiac catheterization in the University Cardiovascular Laboratory (Fig. 1). Activity was moderately limited for the next three months, but he then began experiencing transient anterior chest pain, exertional dyspnea, and paroxysmal nocturnal dyspnea. Three months prior to the present admission, he noted "yellowness of his eyes" and intermittent diarrheal clay-colored stools. Along with these latter symptoms his dyspnea became more intense and necessitated a mercurial diuretic each week. Two weeks before entry and concomitant with an upper respiratory infection, his jaundice deepened and severe pruritus supervened. Twelve days prior to admission he received his last mercurial injection and for the first time obtained no beneficial effect. The dyspnea increased, and at this time the patient was hospitalized.

Past history: Usual childhood diseases admitted. Operations—tonsillectomy and adenoidectomy in childhood. Thorough investigation was of no value in obtaining any signs or symptoms of rheumatic fever. To his knowledge he had never been hypertensive. The review of symptoms and family history was noncontributory.

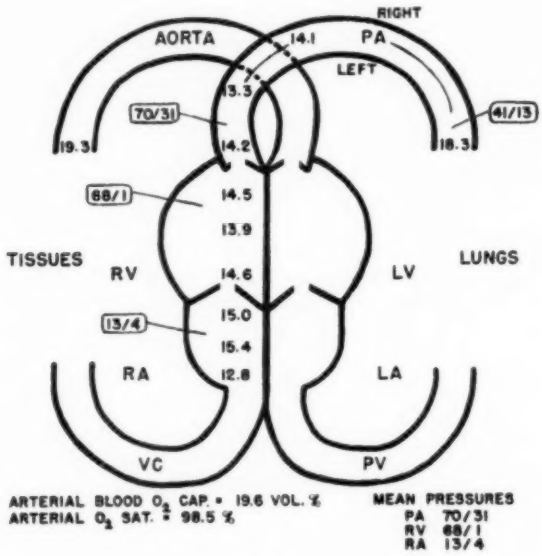

Fig. 1.

Physical examination: Blood pressure, 100/80 mm. Hg; pulse, 104; respiration, 24; temperature, 99.4° F. The patient was a well developed, thin, white man in moderate respiratory distress and with a pale yellow tint to the skin. The conjunctivae were slightly injected, and the sclerae were yellow in color. The fundus of the left eye revealed a few refractile exudates. The lips were faintly cyanotic. There was a suggestion of a nodule on the left side of the thyroid gland. Inspection of the chest disclosed a bulge in the precordial area. The lungs were clear to percussion and auscultation. There was a diffuse heaving of the precordium, and the apical impulse was located 11.5 cm. from the mid-sternal line in the fifth left intercostal space, 2 cm. outside the mid-clavicular line. The right cardiac border was percussed 1.5 cm. to the right of the sternum in the fourth right intercostal space. There was a marked systolic thrill over the precordium which was difficult to localize. The sounds were regular in rate, rhythm, and force. A Grade 4 systolic rumbling murmur was present, heard loudest at the fourth left intercostal space parasternally and transmitted over the precordium to the neck and to the face. P_2 was accentuated, and M_1 was greater than M_2. The abdomen was scaphoid, soft, and not tender. A firm, smooth liver edge descended 7 cm. below the right costal margin in the mid-clavicular line. The spleen was not palpable. The prostate was twice the normal size, and the reflexes were physiologic.

Laboratory data: Hemoglobin, 16.5 Gm. per cent; hematocrit, 53 vol. per cent; white blood count, 9,200 per c.mm. with a normal differential. Urinalysis revealed a specific gravity of 1.022

with 2+ albumin, some white blood cells and red blood cells, and a few hyaline and granular casts. An electrocardiogram disclosed sinus rhythm with broad notched P waves in Leads II, III, aV_F, and V_1, pointing to auricular enlargement. A roentgenogram of the chest on Feb. 22, 1952, revealed the heart to be markedly enlarged, both to the right and left, and it had a somewhat globular configuration. The left cardiac border appeared straight without any prominence of the pulmonary conus. The aortic knob was smaller than normal. Re-examination, including fluoroscopy, on Feb. 24, 1952, demonstrated marked enlargement of the left auricle, but the roentgenologist was unable to give a clear diagnostic impression of the cardiac defect.

Hospital course: Despite the continuation and intensification of cardiac supportive measures, the patient became progressively more cyanotic, edematous, jaundiced, and confused. The patient expired on the twelfth hospital day, after having remained afebrile except for a terminal elevation to 102° F. On the day of death, râles and bronchovesicular breath sounds were audible over the right lower anterior chest. Oxygen saturation studies on Feb. 29, 1952, showed 67.7 per cent saturation which increased to 88.4 per cent after the inhalation of pure O_2.

Gross necropsy findings: The most important observations were limited to the heart. This organ weighed 550 grams and showed evidence of dilatation and hypertrophy of both auricles. The right ventricle measured 1 cm. in thickness and the left ventricle was 1.6 cm. in thickness. The pulmonary artery appeared enlarged and showed an in situ diameter of approximately 3 cm. Examination of the cardiac chambers disclosed dilatation of both the mitral and tricuspid valve rings. Both mitral leaflets were thicker than normal, each measuring about 0.2 cm. in thickness. The free margin of the posterior leaflet was rolled, and there were no chordae tendineae from this leaflet to the papillary muscles (Fig. 2). Both anterior and posterior papillary muscles did, however, send isolated chordae tendineae toward the base of this leaflet in the region of the annulus fibrosus. The undersurface of this posterior leaflet revealed many ridged, raised structures of varying thickness which appeared to be remnants of chordae tendineae (Fig. 3). The thicker filaments tended to be arranged perpendicularly to the annulus while the thinner filaments ran transversely across the valve surface. These abortive chordae tendineae were generally attached at their peripheral portions and were free in their mid-portions. The arrangement of the papillary muscles within the left ventricle was not unusual, and at the apex of the posterior muscle there was a tiny, opaque, raised nodule at the point where the chordae tendineae would normally arise. An interauricular septal defect was present at the anterior margin of the fossa ovalis (ostium secundum). The defect measured 1.5 cm. in diameter, and although it communicated with the left auricle, it tended to be partially covered by a valvelike structure on the left side.

Other significant necropsy findings were the presence of four great vessels arising from the arch of the aorta, recent infarction of the middle lobe of the right lung, recent bilateral renal infarctions, and thrombosis of the left renal vein. No abnormalities were noted within the tricuspid or the semilunar valves, or their attachments.

The microscopic examination of the posterior mitral leaflet confirmed the impression that these structures on the undersurface of the leaflet were rudimentary chordae tendineae. They were composed of bundles of avascular, dense, collagenous connective tissue with a few elastic fibers. No muscle tissue was apparent, and there was no evidence of inflammatory changes. The myocardium showed evidence of nuclear variation in size and shape consistent with the marked hypertrophy. The pulmonary and renal infarctions noted on gross examination were confirmed microscopically.

CASE 2.—C.J., a 72-year-old white man of Danish extraction was admitted to Crouse-Irving Hospital in a state of unconsciousness. It is stated that there had been chest pain of 10 minutes' duration preceding the onset of the unconsciousness. The patient had been a known cardiac individual and was on digitalis for the past 10 to 12 years. In the past there had been ankle edema, chest pain, and high blood pressure. There had been other hospital admissions of short duration for dyspnea and chest pain.

Past history: One year ago the patient was admitted to City Hospital with chills, fever, and cough, and a diagnosis of pneumonia was made at this time. The process resolved under Aureomycin therapy. At this time there was a regular sinus rhythm, normal blood pressure, and the

Fig. 2.

Fig. 3.

Fig. 2.—The thickened posterior mitral leaflet demonstrating a "tented" appearance and absent chordae tendineae.

Fig. 3.—Undersurface of the posterior mitral leaflet showing the raised, ridged remnants of chordal structure.

electrocardiogram disclosed left ventricular enlargement. Since this admission the patient had been fairly well on salt restriction, and 0.1 Gm. of digitalis daily. There had been pedal edema, dyspnea on exertion, and the patient spent much of the time in bed.

Physical examination: Blood pressure, 80/60 mm. Hg; pulse, 80 and irregular; respiration, 24; and temperature, 99.2° F. The patient was a well developed, well nourished white man who was moderately cyanotic, lying in bed moaning occasionally, and responding very sluggishly. Examination of the chest revealed it to be symmetrical and with no evidence of lag or retraction. The

Fig. 4.

Fig. 5.

Fig. 4.—Anterior mitral leaflet showing the two accessory ostia and the chordal attachment about the larger orifice. X2. Reduced one-sixth for journal reproduction.

Fig. 5.—Undersurface of the anterior mitral leaflet showing in detail the attachment of the chordae tendineae about the larger accessory orifice. X2. Reduced one-sixth for journal reproduction.

lungs were clear to percussion and auscultation but the breath sounds were distant. Inspection of the heart disclosed the apical impulse to be in the fifth intercostal space in the mid-clavicular line. The sounds were distant and the ventricular rhythm was very rapid and irregular (140 to 156 with a radial pulse of 80). There was some slowing with carotid sinus pressure. A Grade 2 blowing systolic murmur was audible over the precordium. The abdominal examination was negative, and the extremities were essentially negative. Neurological examination disclosed the deep tendon reflexes to be active, and there was bilateral dorsiflexion on plantar stimulation. Both cremasterics and the left abdominal muscle reflexes were absent. The right abdominal reflex was weak. There was a moderately active bilateral intention tremor of the hands and arms. There was no aphasia or muscle or limb paresis.

Laboratory data: Hemoglobin, 12 Gm. per cent; hematocrit, 40 per cent; white blood cells, 15,400 per c.mm. with 80 per cent polymorphonuclear leucocytes. Urinalysis revealed a specific gravity of 0.015 with a trace of albumin, 5 to 15 white blood cells per high-power field and some cellular and granular casts. The nonprotein nitrogen was 32 mg. per cent, and the cholesterol was 106 mg. per cent. An electrocardiogram disclosed severe S-T depression in Leads I, II, aV_L, aV_F, and V_{1-6} with elevation in aV_R. While the changes were thought to be due to the tachycardia plus digitalis effect, an acute subendocardial infarction could not be ruled out.

Hospital course: The hypotension persisted and the patient remained disoriented. He expired on the third hospital day.

Gross necropsy findings: The significant findings were limited to the heart and lungs. The heart, which weighed 420 grams, disclosed moderate left ventricular hypertrophy. Examination of the mitral valve revealed two foramina within the anterior cusp (Fig. 4). The larger of these foramina was elliptical in shape and measured 1 x 0.5 cm. It was oriented perpendicular to the mitral annulus and one margin was located at a distance of 0.6 cm. from the free border of the valve. There was no thickening of the valve substance, and there were no rudimentary cusps present about the foramen. Examination of the undersurface (ventricular) of the cusp disclosed the presence of fine filamentous chordae tendineae which inserted circumferentially about the margins of the foramen (Fig. 5). These fine filaments extended from the foramen margin a distance of 1 cm. at which point they converged into a single chorda tendinea. The latter inserted normally into the apex of the anterior papillary muscle. The second perforation was much smaller, measuring 0.2 cm. in diameter and was located 0.8 cm. from the larger towards the septum. Its undersurface showed the same peculiar filamentous chordal attachment in a circumferential manner. The two papillary muscles were normal in size and in arrangement. The aortic cusps showed fusion of their leaflets and there was moderate calcium deposition within their substances and at their basal portions. There were two ostial openings for the right coronary artery but the coronary arteries showed minimal atherosclerotic changes. Nothing suggestive of old or recent myocardial infarction was noted. Other necropsy findings were extensive bilateral lobular pneumonia and a small gastric polyp. The examination of the brain disclosed nothing unusual.

Microscopic examination disclosed the anterior cusp of the mitral valve to be composed of the usual loose connective tissue structure. No variation in pattern was noted about the margins of the foramina and there was nothing suggestive of inflammatory changes. The entire leaflet was slightly more vascular than usual and the chordae tendineae and papillary muscles were not remarkable. The heart muscle showed evidence of hypertrophy, and there was moderate coronary artery atherosclerosis. Other microscopic findings of interest were the calcified aortic cusps, bilateral lobular pneumonia, and a benign gastric polyp.

DISCUSSION

The detailed development of the atrioventricular valves and their appendages is a somewhat neglected subject in the standard textbooks of embryology.[1,7] Their development, according to Arey,[7] is bound up with the endocardial cushions which by fusion and figure-of-eight pattern, convert the single atrioventricular canal into two canals. Elevated folds of endocardium appear at the margins of

these canals and each set of thickenings becomes both invaded by muscle and attached to the muscular trabeculae of the ventricular wall. Mall[8] states that the atrioventricular cushions expand not only by their own growth but to a greater extent by a process of undermining the ventricle wall around the venous ostia. The extent to which this burrowing has occurred is marked by the attachment of the valves to the muscle walls of the heart. The tendons nearest the tips of the valves were first to form while those nearer the bases of the valves were formed subsequently. This process of undermining the attachment of the base of the valve to the wall of the ventricle telescopes the atrial portion into the ostia. The muscle of the atrium extends into the atrial part of the valves, which at first is continuous through the tendinous cords with the ventricular muscle. At first the atrioventricular muscle connection is through the main wall of the ventricle, but as this is resolved into the trabecular system with the growth of the valves and the formation of the papillary muscles, the connection between atrium and ventricle is through the tendinous cords which are at first muscular. Later with the degeneration of the muscle of the cords, the muscular connection between atria and ventricles is believed to have been broken down completely. Although the muscle connection between atria and ventricles remains through life in lower vertebrates, in man the cords are converted into connective tissue but the muscle may extend well into the valves. The muscular connection through the valves is first interrupted at the free thin edges and later the muscular fibers in the tendinous cords disappear. Since the developmental processes which Mall[8] has so clearly described are stated to be complete in the 30 mm. human embryo, we must assume that some exaggeration in the undermining process occurred in the first case herein reported at this early date in embryonic life. It is to be noted that no remnants of muscle tissue were identified within the malformed chordae tendineae on the undersurface of the mitral leaflet. The second case which is reported in this paper, the so-called "duplication of the mitral valve," has been explained both by a developmental malformation and by an inflammatory origin.[6] There appears to be very scant evidence to support an inflammatory origin for this abnormality, and according to Abbott[9] the most tenable theory is that of fenestration of the endocardial cushions in early embryonal life with transformation into a second mitral orifice and adaptive growth of papillary muscle and chordae.

The infrequency of congenital abnormalities of the mitral leaflets can be best appreciated from reviews of the incidence of congenital heart disease at some of the larger centers. Investigators from the Mayo Clinic,[10] in a series of 8,314 unlimited post-mortem examinations including those performed on premature and stillborn infants, found eighty-seven instances of major cardiac congenital anomalies. In this series although there were several cases of both deficiency and excess of the aortic and pulmonary cusps, there is no mention of mitral valve malformations. Jacobius and Moore[11] in reviewing 1,600 necropsies at the New York Hospital from November 1931 to June 1937, found 131 congenital cardiac anomalies (8.1 per cent). In this series there were four cases of mitral stenosis, four of segmentation of the anterior leaflet of the mitral valve, and one instance of an anomaly of the posterior papillary muscle. Abbott,[5] in presenting the

statistics concerning 1,000 cases of congenital cardiac disease which she had analyzed (p. 60), lists six instances of anomalous chordae within the ventricles, none of which died a cardiac death. In her discussion of anomalies of the endocardium (p. 24) she states that aberrant chordae tendineae are of interest from the diagnostic standpoint on account of the confusing signs they are likely to produce but are unimportant otherwise. It is to be emphasized that Abbott is obviously referring to cases of anomalous insertion of the chordae tendineae, hardly comparable with Case 1 reported herein in which the entire leaflet was devoid of anchoring chordal attachment. It is of interest that a review of the literature dealing with congenital cardiac anomalies, including a number of cases of mitral atresia, has failed to disclose an instance similar to the first case herein reported.

Schraft and Lisa,[6] in a review of the literature dealing with mitral valve duplication, point out that of a total of twelve reported cases, all have been found incidentally at necropsy and none have been associated with clinical manifestations attributable to the defect. In general, these cases are characterized by a single ovoid accessory ostium in the anterior mitral leaflet. About the margins of this defect, the typical case reveals differentiated leaflets which attach by slender, perfectly formed chordae to papillary muscle on the anterior ventricular wall. Microscopic evidence of inflammatory changes within the valve or about the accessory ostium has not been convincing. Case 2 differs from the typical case in that instead of a duplication, its three orifices make it actually a "triplication" of the mitral valve. It is also somewhat unique because there is no suggestion of attempted cusp formation about the margins of the defects.

SUMMARY

Two unusual abnormalities of the mitral valve and its appendages have been described. The mitral valve "triplication" was an incidental finding at necropsy in a 72-year-old man while the other case, a severe dysplasia of the chordae tendineae, permitted the individual to survive until the age of 26 years. Because of the infrequent occurrence of congenital anomalies of the mitral valve, the clinical and pathological aspects of these two cases have been presented in some detail.

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ANATOMIC VARIATIONS IN THE TETRALOGY OF FALLOT

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THERE are two types of congenital pulmonary stenosis. The type most frequently encountered is that present in tetralogy of Fallot, in which the pulmonary stenosis is accompanied by a defect of the interventricular septum, overriding aorta, and hypertrophy of the right ventricle. The second, less frequent type is that in which the pulmonary stenosis occurs with intact interventricular septum. It is obvious that, in this situation, overriding of the aorta cannot occur.

In the tetralogy of Fallot, Blalock and Taussig[1] devised a shunt operation to increase the flow of blood to the lungs. This was achieved by an end-to-side anastomosis between the subclavian and pulmonary arteries. A modification of this technique was introduced by Potts and associates,[2] in which a direct anastomosis was carried out between the aorta and the pulmonary artery. Relief of symptoms by these procedures has now been well established in large groups of patients.

In pulmonary stenosis with intact interventricular septum, the shunt operation is contraindicated. It fails to relieve the overburdened right side of the heart and increases the load upon the left side because of the greater amount of blood delivered to the left atrium. Sellers[3] and Brock[4] introduced intracardiac pulmonary valvulotomy for the relief of this condition, and the results have been most gratifying. Inasmuch as the pulmonary stenosis is usually valvular, and there is no narrowing of the infundibulum, a transventricular approach to the valve is unhampered.

Since then, Brock[5] has sought to apply the intracardiac approach to the tetralogy of Fallot. On re-evaluating the anatomy of his cases of tetralogy of Fallot, he noted that, contrary to previous opinion, a significant number had stenosis of the pulmonary valve as the primary point of obstruction to pulmonary blood flow. In such instances pulmonary valvulotomy would be feasible. In the remaining cases, he felt that the infundibular obstruction, usually present in the tetralogy of Fallot, was such that it could be relieved by excision or dilation of the obstructing ventricular musculature. There is, however, considerable variation in the anatomy of the infundibulum and the pulmonary valve

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in cases of tetralogy of Fallot. It is important to know whether these variations offer serious or insuperable difficulties to direct attack in a significant percentage of cases.

It is readily appreciated that the study of the heart post mortem, in which the majority of the specimens must be fixed with resultant shrinkage and distortions of contour, may fail to portray with complete accuracy the situation which existed in the living heart. Yet the variations thus observed must give at least a rough idea of the conditions which existed during life. At the present time, there is a difference of opinion as to the relative merits and dangers of direct approach to the pulmonary valve compared to a shunt operation in the tetralogy of Fallot. The purpose of this paper is to record observations bearing upon this subject.

At the onset, some fundamental concepts should be reviewed. In the normal heart, a band of muscle called the *crista supraventricularis* is present along the posterior wall of the right ventricle and extends from the base of the pulmonary artery to the tricuspid valve. It represents a portion of the conus arteriosus which meets the interventricular septum in the embyro to complete the separation of the right and left ventricles. Normally, the wall of the conus partially atrophies to establish a patent pulmonary outflow tract. In the tetralogy of Fallot, however, this muscle does not atrophy adequately. It shifts laterally, closer to the anterior wall of the right ventricle, forming a stenotic outflow tract from the main chamber of the right ventricle to the pulmonary artery. The stenotic outflow tract is called the *infundibulum*. The orifice at the inferior end of the infundibulum is known as the *ostium*. Above the ostium, the outflow tract frequently is dilated and is called the *infundibular chamber*, the "conus" or the "third ventricle." The *crista supraventricularis* forms the media wall of the infundibulum. The posterior wall is formed by the main interventricular septum, and the anterior wall is formed by the anterior wall of the right ventricle.

MATERIALS AND METHODS

From a post-mortem collection of approximately 350 congenital malformations of the heart at The Children's Memorial Hospital, forty-two specimens fulfilled the criteria for tetralogy of Fallot. Six of these were examined within 8 hours after death, and the remainder had been fixed in formalin for variable periods of time prior to analysis.

Stenosis of the pulmonary valve, when present, was in all instances associated with some degree of infundibular deformity. Twelve specimens had atresia of the pulmonary valve, the infundibulum, or the entire main pulmonary artery (Table I). These hearts were not studied extensively because at the present time there is agreement that a systemic pulmonary shunt is the only possible procedure in this type of malformation. The remaining thirty hearts had patent pulmonary arteries associated with stenosis of the infundibulum and were candidates for either resection or systemic pulmonary anastomosis. These hearts were analyzed by two methods:

TABLE I. TYPES OF OBSTRUCTION OF PULMONARY BLOOD FLOW IN FORTY-TWO POST-MORTEM SPECIMENS OF TETRALOGY OF FALLOT

	PATIENTS
Atresia of the pulmonary artery	
Complete	8
Partial	4
Stenosis of the pulmonary valve without infundibular deformity	0
Infundibular stenosis, with patent pulmonary artery, with or without pulmonary valvular stenosis	30

1. A paraffin mold was made of the interior of the right ventricle, infundibulum, and pulmonary artery to a point just proximal to its bifurcation. The paraffin was injected under pressure and the mold was measured. This method was fairly successful in the fresh specimens but was of little value in the fixed hearts.

2. By means of a flexible ruler, the circumference at the region of greatest stenosis was measured. Other anatomic features were also determined, such as the length of the infundibulum, the distance from the stenotic point in the infundibulum to the pulmonary valve cusps, the circumference of the pulmonary valve ring, the size of the interventricular septal defect, and the amount of aortic overriding.

RESULTS

It must be remembered that in any study of tetralogy of Fallot the grouping of hearts is difficult. In this series no two hearts were alike. Indeed, each specimen could be easily recognized and segregated. Any attempt, therefore, to classify these malformations must necessarily be quite arbitrary and there will always be a gradual transition of one group into another. Nevertheless, the thirty hearts utilized for extensive study were divided into five groups, each group consisting of a variable number of hearts with relatively similar infundibular pathology (Table II).

TABLE II. CHARACTERISTICS OF INFUNDIBULAR STENOSIS WITH PATENT PULMONARY ARTERY (30 SPECIMENS)

TYPE OF STENOSIS	PATIENTS	(%) *	PATIENTS WITH VALVULAR STENOSIS	DEGREE OF OVERRIDING OF THE AORTA		AGE DISTRIBUTION					
				RANGE (%)	MEAN (%)	0-4 MO.	5-12 MO.	13-24 MO.	25-36 MO.	3-10 YR.	OVER 10 YR.
Band Stenosis	8	19.0	1	10-50	25	—	1	4	—	1	2
Subvalvular stenosis	3	7.0	0	10-50	30	—	—	—	3	—	—
Intermediate Stenosis	4	9.5	1	30-60	45	—	—	2	—	1	—
Tubular Stenosis	10	24.0	4	15-80	60	4	1	3	—	1	—
Compensated Stenosis	5	12.0	4	15-55	40	1	3	—	—	1	—

*These percentages do not include the group with atresia of the pulmonary artery.

Group 1. Band Stenosis (Eight hearts or 19.0 per cent of the series, Figs. 1 and 2).—In this group, the maximum infundibular stenosis was caused by a thin fibromuscular band at the ostium of the infundibulum. Immediately above this band, the infundibulum widened into a poststenotic dilated outflow chamber. This poststenotic "third ventricle" or "conus" varied in diameter, usually in proportion to the size of the stenotic ostium, the greater the stenosis, the greater the dilatation. In contrast, the distance from the stenotic band to the pulmonary valve was quite variable and followed no definite pattern. There was severe valvular stenosis in only one instance. Of the remaining specimens, the pulmonary valve was bicuspid in five specimens and tricuspid in two. The pulmonary artery was hypoplastic in the one heart with valvular stenosis, small in four hearts, and of good caliber in three. A postvalvular dilatation of the pulmonary artery was present in three instances.

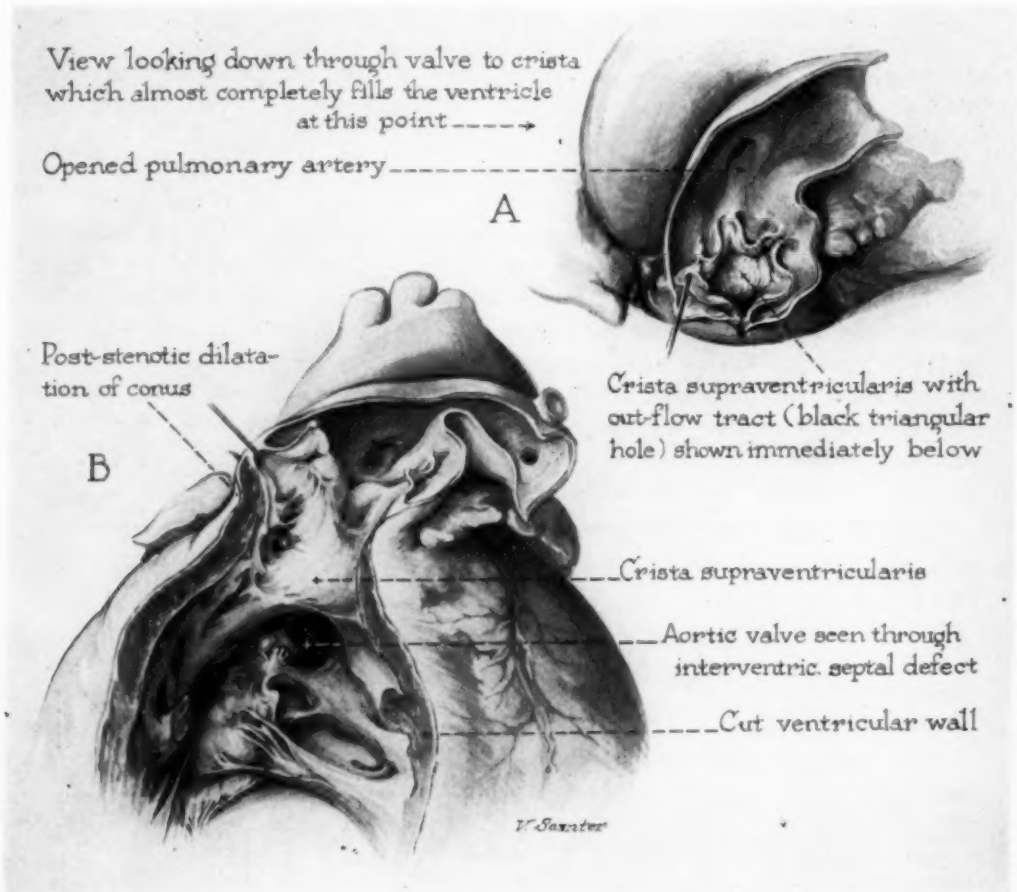

Fig. 1.—This 28-month-old white girl developed acute bacterial endocarditis and, after treatment with antibiotics, received an aortic pulmonary anastomosis. The endocarditis recurred and the patient expired. Note the obstructing fibrous band at the inferior end of the infundibulum.

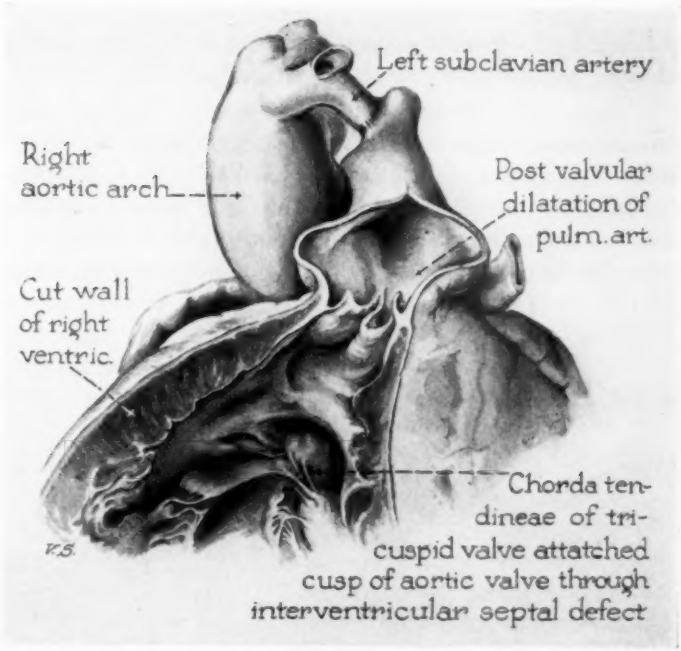

Fig. 2.—This 23-month-old white girl had severe convulsions since the age of three weeks. She had a subclavian pulmonary anastomosis, and on the second postoperative day, she convulsed, developed left hemiplegia, and died. As in the first case, the primary point of obstruction is a fibrous band at the ostium of the infundibulum.

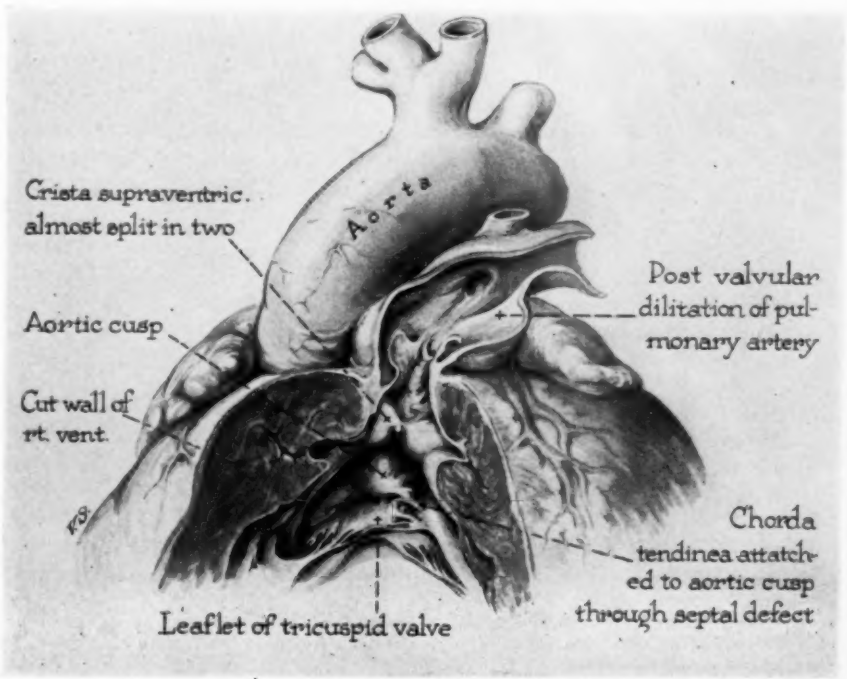

Fig. 3.—This 2½-year-old white girl began to avoid all physical exertion and to lose consciousness periodically. Following an aortic pulmonary anastomosis, a respiratory infection developed. She died with bilateral pneumonitis and passive congestion of the lungs and liver. Note the short infundibulum and the stenotic band just below the base of the pulmonary artery.

The hearts belonging to this group were taken, in general, from older patients (Table II). They had the least severe degree of overriding, averaging about 25 per cent and were probably the most amenable to direct intracardiac surgery.

Group 2. Subvalvular Stenosis (Three cases, or 7.0 per cent of the series, Fig. 3).—Subvalvular stenosis is hardly an accurate name for this type of anomaly. However, it is used for lack of a better term. The crista supraventricularis was almost completely atrophied, having only a bandlike ridge impeding blood flow at a point immediately below the pulmonary valve. A bicuspid pulmonary valve and postvalvular dilatation of moderate degree was noted in all specimens. Overriding of the aorta was fairly severe, averaging 35 per cent from the right ventricle.

This type of anomaly would probably be amenable to incision and dilatation of the subvalvular stenosis. It is important to note, however, that the

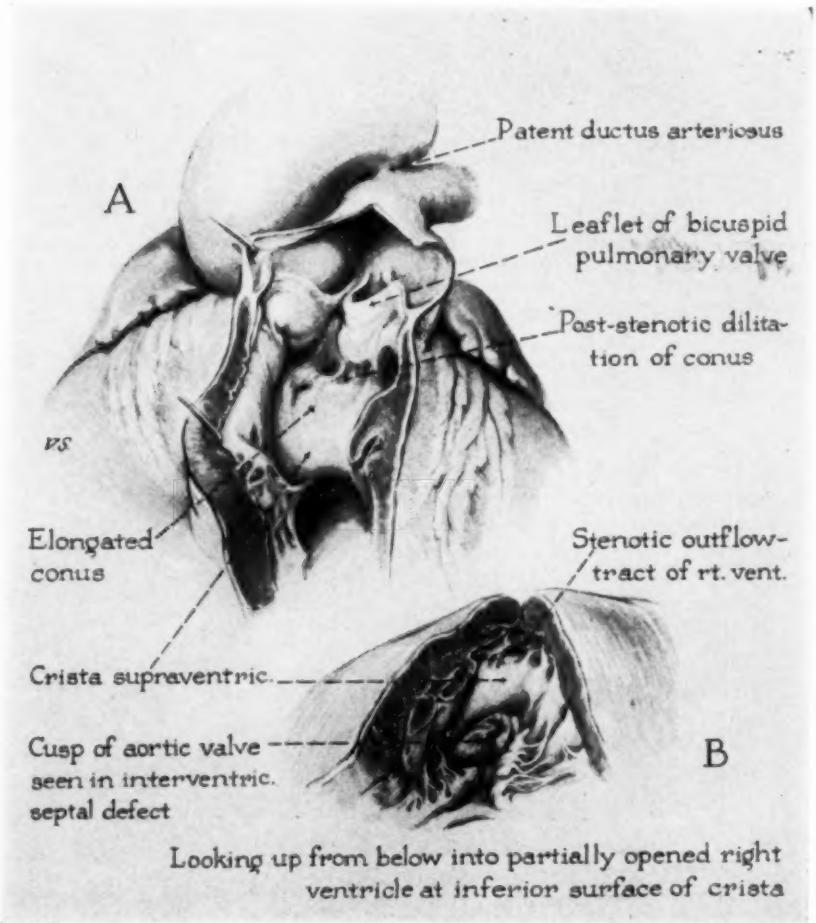

Fig. 4.—About three weeks before admission, this 24-month-old white girl began to lose consciousness every few minutes. She refused to do any physical exertion. Following an uneventful aortic pulmonary anastomosis, she developed generalized convulsions and expired. Note (*A*) that the obstruction to pulmonary blood flow consists of a mound of muscles at the lower end of the infundibulum. Note also (*B*) the intimate association of the aortic valve cusps with the *crista supraventricularis*.

band of remaining crista supraventricularis is the only remnant separating the pulmonary artery and aorta at the base of the heart. It also supports one of the aortic valve cusps. Incision of the crista would jeopardize the aortic cusp and might create an aortic pulmonary septal defect.

Group 3. Intermediate Stenosis (Four hearts or 9.5 per cent of the series, Figs 4. and 5.—In this group were placed the specimens in which the main barrier to adequate blood flow was the projecting "humplike" crista supraventricularis. This mound of cardiac muscle, covered usually by a thick layer of endocardial fibroelastic tissue, formed an obstruction varying from 5 mm. to 10 mm.

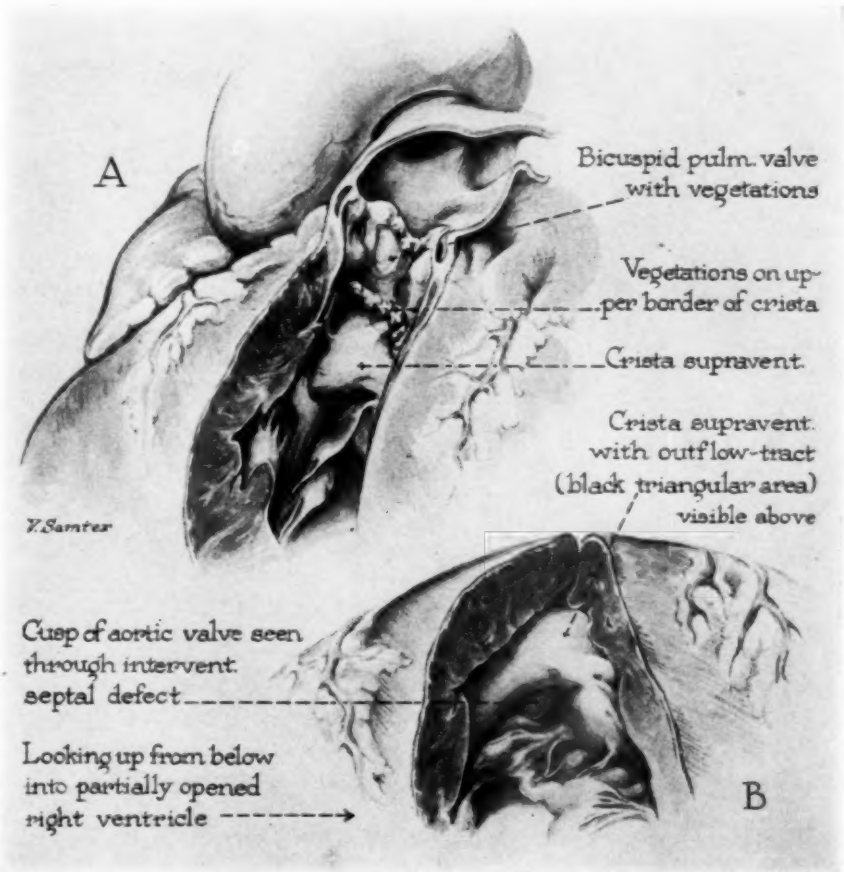

Fig. 5.—This 5-year-old child had an exploratory thoracotomy and expired in the immediate postoperative period. Note the large muscular mound obstructing the inferior portion of the infundibulum. Severe valvular stenosis and vegetations in the dilated infundibular chamber are also present.

in length. Between the crista supraventricularis and the pulmonary valve a small poststenotic dilated space was present. Associated with the thick projecting crista, there was an area of greatest stenosis at the ostium of the infundibulum, in the subvalvular region, or at the valve. In one instance (Fig. 5), severe stenosis existed in all three regions. To obtain an adequate pulmonary blood flow in the intermediate stenoses, a large mass of cardiac muscle must be rongeured away from the crista supraventricularis.

Group 4. Tubular Stenosis (Ten hearts, 24.0 per cent of the series, Fig. 6).—This group consisted of the specimens with tubular infundibular stenosis. The infundibulum was long and narrow throughout its entire length. There were often slightly raised regions within the long narrow tube, followed by shallow depressions which gave this chamber a loculated appearance. In general, even

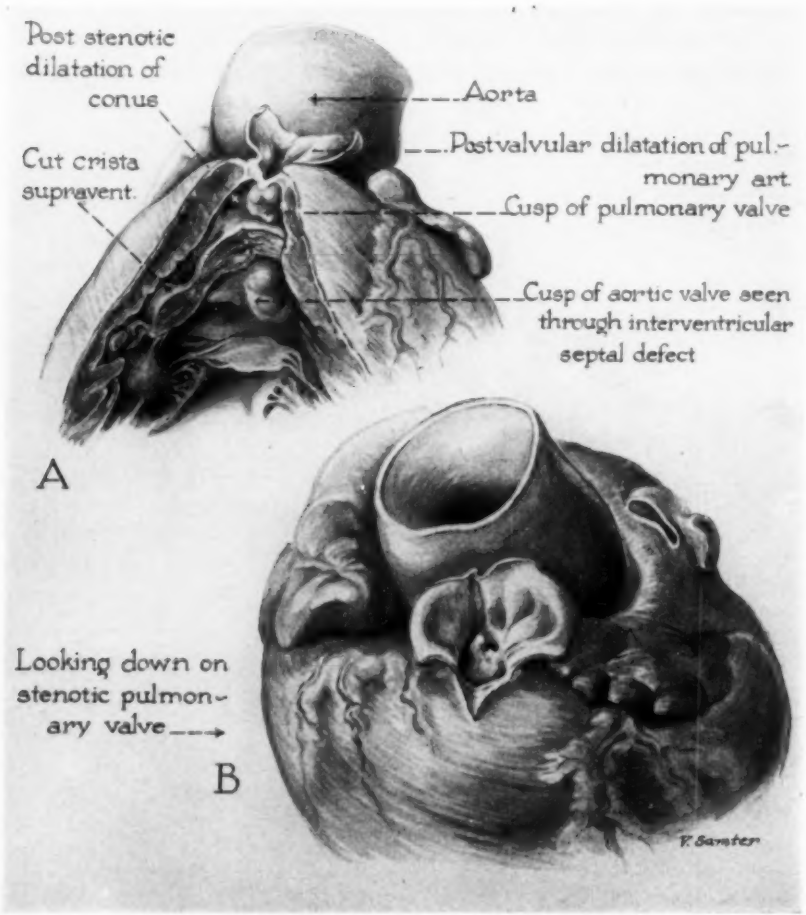

Fig. 6.—This 14-month-old white boy was severely cyanotic since birth. He had not been able to sit or walk. Growth had been poor. Surgery was contemplated but the patient developed a severe respiratory infection and expired. Note the severe tubular stenosis of the infundibulum, associated with severe valvular stenosis.

the most dilated part of the outflow tract was of such small caliber that an adequate pulmonary blood flow could have been obtained only by the removal of the entire infundibulum. Pulmonary valvular stenosis of severe degree was associated in four instances. In all these specimens, the pulmonary artery was small or hypoplastic. These hearts came from the younger children (Table II) and were probably not amenable to direct intracardiac surgery. Overriding of the aorta averaged 60 per cent from the right ventricle.

Group 5. Compensated Stenosis (Five cases, 12.0 per cent of the series, Fig. 7).—This group was composed of malformations in which the anterior part of the crista supraventricularis was split, forming a defect through which blood could flow from the region of the interventricular spetal defect into the upper conus, by-passing the normal outflow tract or lower infundibulum. In all instances, the lower infundibulum was almost completely occluded by the more apical portion of the split crista supraventricularis. Massive resection of the crista would have been necessary to provide an adequate outflow tract from the

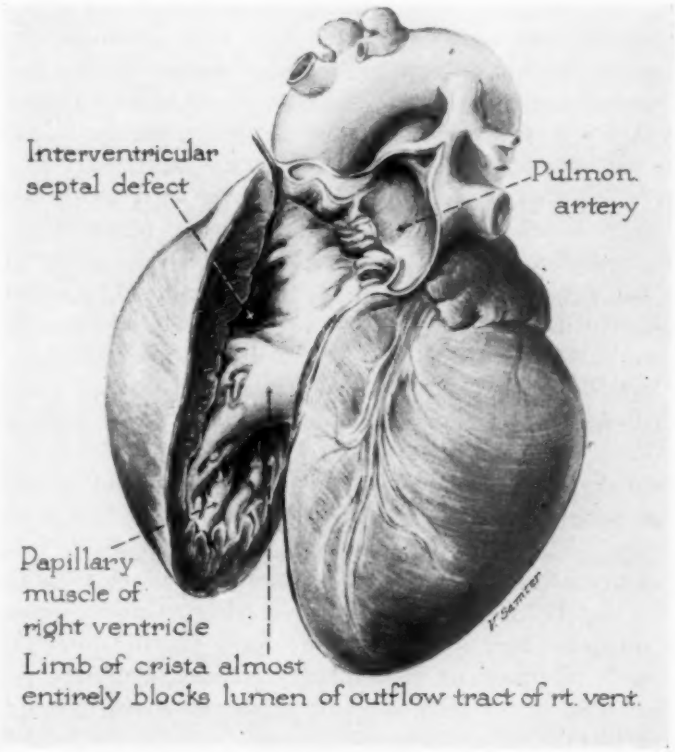

Fig. 7.—This one-month-old infant had a right aortic arch with a patent ductus arteriosus which formed a vascular ring about the trachea. She also had a complete right harelip and cleft palate. She was admitted with severe pneumonitis and expired. The large *crista supraventricularis* is split, permitting blood to be shunted from the region of the intraventricular septal defect to the pulmonary artery. However, to accomplish an adequate flow of blood to the lungs, the massive crista would have to be resected.

right ventricle. In four cases there was an associated valvular stenosis with a hypoplastic pulmonary artery. The remaining specimen had a tricuspid pulmonary valve and a normal pulmonary artery.

DISCUSSION

It is evident that the results obtained in this study differ significantly from those obtained by Brock and Campbell[6,7] and by Glover and associates.[8] In

order to attempt an explanation of these differences, one must of necessity analyze the salient anatomic and statistical findings in this paper.

Infundibular Stenosis.—Pulmonary infundibular deformity was present in every specimen examined and was associated with a variable degree of infundibular stenosis. The infundibular stenosis in some instances was minimal, due to the extreme shortening of the crista supraventricularis. In all cases, however, the infundibular stenosis was the primary pathology and it is to this structure that treatment would have had to be directed.

The least amenable to intracardiac surgery were the specimens with atresia and the hearts in Groups 4 and 5. These comprised 64 per cent of the series. None of the twelve cases of atresia would have been benefited by infundibular resection, since the infundibulum was completely sealed off from the lungs by obliteration of the pulmonary artery at the base of the heart. Four of these cases had a large enough segment of pulmonary artery to permit a shunt operation. The rest were not amenable to any type of surgical treatment.

The hearts in Group 4 had tubular stenosis of such severe degree that the entire crista supraventricularis would have had to be removed, a very difficult and traumatic procedure. The hearts in Group 5 were slightly more amenable to direct cardiac surgery. In four of the five specimens, it would have been necessary either to increase the size of the defect in the split crista supraventricularis or to remove the lower portion of the infundibulum. This again would be a formidable procedure. In addition, the task of making a correct diagnosis of compensated infundibular stenosis in vivo seems almost impossible at present.

The hearts in Groups 2 and 3 (23 per cent of the series), although amenable to intracardiac surgery, had certain anatomic features which could complicate such a procedure. The subvalvular stenosis could be easily incised and dilated through an intraventricular approach. However, one must not overlook the hazard of injuring the aortic valve or of creating an aortic pulmonary septal defect, when this procedure is done without direct visualization. The specimens in Group 3, with intermediate infundibular stenosis, could be relieved by infundibular resection, but a large amount of tissue would have to be removed before adquate blood flow could be established.

The hearts most amenable to direct cardiac surgery were found in Group 1 and comprised 19 per cent of the series. In those specimens, the bandlike stenosis at the lower portion of the infundibulum associated with a dilated infundibular chamber above the point of obstruction made intracardiac resection of the infundibular stenosis feasible.

Valvular Stenosis.—Valvular stenosis was present in ten cases or one-third of the specimens with patent pulmonary arteries (Table II). It was severe with an associated hypoplastic pulmonary artery in eight instances and was most frequently found in Groups 4 and 5. Although stenosis of the pulmonary valve without an associated infundibular deformity has been reported by others,[6,9] it was always associated with severe infundibular stenosis in this series.

Pulmonary Artery.—Poststenotic dilatation of the pulmonary artery was moderate in ten specimens, slight in fourteen, and absent in six. A hypoplastic

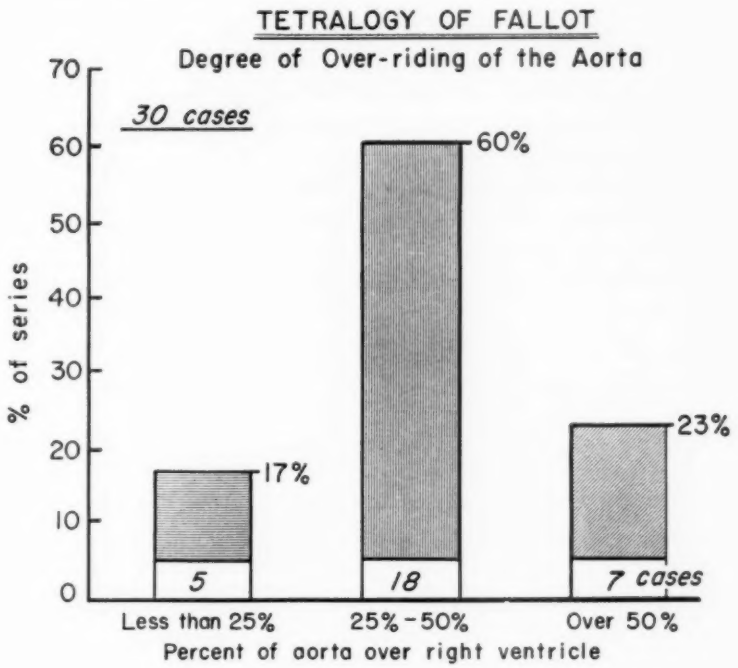

Fig. 8.—Severity of overriding of the aorta. Note that only 17 per cent of the hearts had 25 er cent or less of the aorta overriding the right ventricle. Sixty per cent had between one-fourth and one-half and 25 per cent had over one-half of the aorta overriding the right ventricle.

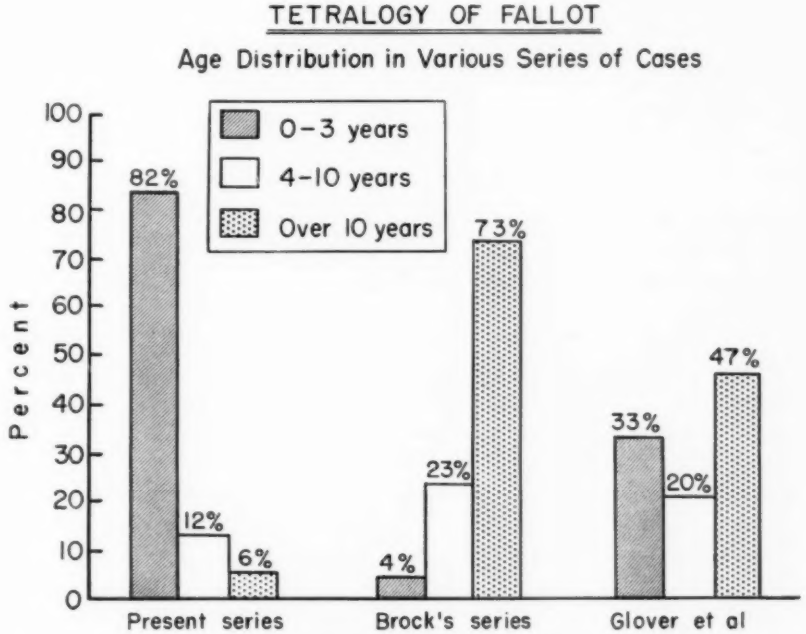

Fig. 9.—Age distribution of patients in various series. Our series had 82 per cent of patients under 3 years of age while the other two series contained the majority of patients over 3 years of age. The patients in our series probably represent very severe forms of tetralogy of Fallot.

pulmonary artery was noted in eleven hearts. All the hearts with a hypoplastic pulmonary artery had an associated severe infundibular stenosis.

Overriding Aorta.—Aortic overriding was severe in the majority of specimens, varying from 15 per cent to 80 per cent and averaging about 50 per cent (Fig. 8). In general, the more marked the overriding, the more severe the infundibular stenosis and the greater the probability of a hypoplastic pulmonary artery. In such patients with severe overriding of the aorta and a small pulmonary artery, one wonders how much the shunt of blood from right to left would be decreased by the removal of the infundibular obstruction.

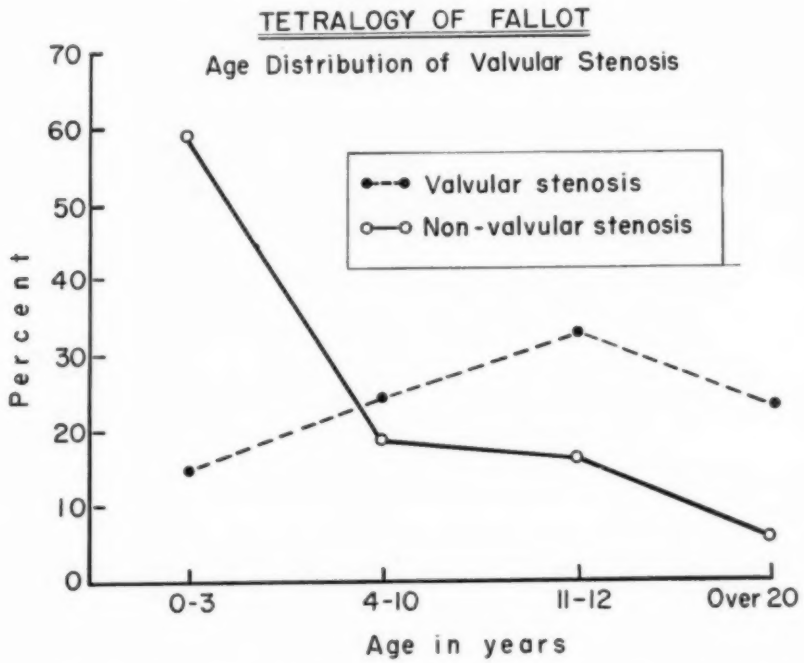

Fig. 10.—Influence of age upon type of obstruction to pulmonary blood flow. One-hundred eleven cases from the literature are tabulated according to age and valvular or nonvalvular obstruction to blood flow. Note that the older the population sample, the higher the relative incidence of valvular stenosis. The incidence of nonvalvular stenosis drops precipitously after the age of 3.

Variations between this series and others[6,7,8] may be at least partially explained by age differences in the patients whose hearts were studied. Obviously, the more severe cases of tetralogy of Fallot will die at a younger age, and since 82 per cent of our series died at less than 3 years of age, they undoubtedly represent the anomalies least compatible with longevity. On the other hand, those anomalies most compatible with life, that is, over three years of age, make up 96 per cent of Brock's series and 67 per cent of Glover's series (Fig. 9). We have not had an opportunity to study such older hearts, but it would seem from the observation of Brock and Glover that they have a higher incidence of valvular stenosis and less severe infundibular deformities. This view is substantiated by a tabulation of 111 cases collected from the literature[6,8,10,11] comparing the age of the patient with the type of obstruction to pulmonary blood flow (Fig. 10).

SUMMARY AND CONCLUSIONS

1. Forty-two specimens of tetralogy of Fallot available in the laboratory of The Children's Memorial Hospital were classified into groups with relatively similar infundibular anatomy, with a view to evaluating the relative applicability of intracardiac infundibular resection and the shunt operations to each of these groups.

2. Twelve specimens had pulmonary atresia, four of these having an adequate pulmonary arterial segment to permit a shunt operation. Of the remaining thirty hearts, which had infundibular stenosis and patent pulmonary arteries, twenty-two were probably not amenable to intracardiac surgery at this time. Eight hearts, however, had a type of infundibular deformity in which intracardiac surgery seemed feasible. These comprised 19 per cent of the series.

3. All hearts with pulmonary valvular stenosis were accompanied by infundibular deformity and, in most instances, had associated hypoplastic pulmonary arteries.

4. Most specimens had moderate or severe overriding of the aorta.

5. Eighty-two per cent of this series was comprised of hearts taken from children under 3 years of age. These specimens probably represented more severe types of tetralogy of Fallot. Other studies, with findings differing from ours, were done mainly on older children and adults. The difference in ages may account, in part, for the difference in pathologic findings.

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THE ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE AND MITRAL STENOSIS*

A Correlation of Electrocardiographic Patterns With Right Ventricular Pressure, Flow, and Work

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FOLLOWING a previous study[1] in which the electrocardiographic patterns of forty-four patients with congenital heart disease were compared with levels of right ventricular pressure and work, a similar analysis of patients with rheumatic heart disease and mitral stenosis was undertaken. Striking differences were noted in the two groups in both the electrocardiographic patterns themselves and in the relationship of these patterns to levels of right ventricular pressure and work. This communication will analyze these differences.

MATERIAL AND METHODS

The material was selected from a series of 350 patients studied at the Los Angeles County Hospital by means of cardiac catheterization according to the technique of Cournand and associates.[2] Of this group, fifty-five patients with rheumatic heart disease and mitral stenosis and sixty-four patients with congenital heart disease were chosen. All had a right ventricular systolic pressure greater than 30 mm. mercury. The assumption was made that elevated right ventricular pressure and/or increased right ventricular work indicated the presence of right ventricular hypertrophy. Patients with evidence of left ventricular hypertrophy were excluded. No patient with a mitral systolic murmur greater than Grade 1 (Levine) was included.

Electrocardiographic measurements and calculations of right ventricular pressure, flow, and work have been reported in a previous paper.[1] In classifying the electrocardiograms, the criteria of Myers and associates[3] were employed; the normal standards of Sokolow and Friedlander[4] and Leatham[5] for adults, and Switzer and Besoain[6] for children were utilized.

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RESULTS

Analysis of the Electrocardiographic Patterns.—Sixty-four patients with congenital heart disease were found to have right ventricular hypertrophy by cardiac catheterization. Sixty-one of these, (91 per cent), had abnormal electrocardiographic tracings; thirty-three showed the electrocardiographic pattern of right ventricular hypertrophy and twenty-eight showed the pattern of partial right bundle branch block. There were three normal tracings.

Fifty-five patients with rheumatic heart disease and mitral stenosis were found to have right ventricular hypertrophy by cardiac catheterization. Twenty-eight of these (51 per cent) had abnormal electrocardiographic tracings; nineteen showed the pattern of right ventricular hypertrophy and nine showed the pattern of partial right bundle branch block. Twenty-seven patients had normal tracings.

Table I lists the salient electrocardiographic features in the precordial leads in both the patterns of hypertrophy and partial right bundle branch block for the two groups. The mean height of R (or R′), the depth of S, the mean durations of the preintrinsicoid deflection times, and the mean R/S ratios are recorded for V_{3R}, V_1, V_5 and V_6.

Tracings showing the electrocardiographic pattern of right ventricular hypertrophy showed clear-cut differences in the two groups. In congenital heart disease the mean R V_{3R} was almost three times the height of R V_{3R} in mitral stenosis. R V_1 in congenital heart disease was about twice as high as in mitral stenosis. The R/S ratio in V_{3R} was approximately three times as great; the preintrinsicoid deflection time in V_1 was longer. Over the left ventricle the mean height of R was similar in both groups. Again, in comparing the R/S ratios over the left ventricle the marked difference between congenital heart disease and mitral stenosis was apparent. The differences were entirely due to the deeper S in V_5 and V_6 in congenital heart disease.

Similar differences were present in comparing the two groups of patients with partial right bundle branch block. In both V_1 and V_{3R} the mean height of R′ was approximately three times as great in congenital heart disease as in mitral stenosis.

The groups with "normal" electrocardiograms are not included in Table I. Three electrocardiograms in congenital heart disease were entirely normal. The twenty-seven electrocardiograms in mitral stenosis, although not falling within the criteria for right ventricular hypertrophy of Myers and associates,[3] nevertheless often had certain abnormal features such as R/S ratios in V_1 and V_{3R} just under one, or slightly delayed preintrinsicoid deflection times over the right ventricle. However the most notable feature of these tracings was the presence of the criterion of Rasmussen and Boe[7]: a small notched or slurred R wave, with a tiny to absent S wave in standard Lead I. This finding was present in fifteen of the twenty-seven "normal" mitral tracings and in twelve of the twenty-eight abnormal mitral tracings. This finding was not present in any tracing in congenital heart disease.

Finally, in Table I the tracings of the entire sixty-four patients with congenital heart disease are compared with the total series with mitral stenosis. The discrepancy between the two groups is greater than ever, as shown, for example, in comparison of the height of R_{V_1}, since the "normal" mitral group has now been added.

TABLE I

		MEAN VALUES OF MEASUREMENTS IN ABNORMAL ELECTROCARDIOGRAMS			
		RIGHT VENTRICULAR HYPERTROPHY		PARTIAL RIGHT BUNDLE BRANCH BLOCK	
		CONGENITAL (33 CASES)	MITRAL (19 CASES)	CONGENITAL (28 CASES)	MITRAL (9 CASES)
V_{3R}	R	14.3 ± 1.7*	5.4 ± 0.95	9.2 ± 1.2	3.5 ± 0.9
	S	1.9 ± 0.6	1.1 ± 0.50	1.8 ± 0.3	0.7 ± 0.2
	R/S	11.79 ± 1.70	4.13 ± 1.01	7.14 ± 1.17	3.24 ± 0.87
	P.D.T.†	0.036 ± 0.002	0.027 ± 0.003	0.050 ± 0.003	0.043 ± 0.005
V_1	R	15.7 ± 1.6	7.6 ± 0.7	10.9 ± 1.5	2.8 ± 0.6
	S	3.1 ± 0.9	1.6 ± 0.5	2.5 ± 0.6	2.9 ± 1.2
	R/S	11.52 ± 1.72	6.47 ± 0.99	8.81 ± 1.63	1.72 ± 0.50
	P.D.T.†	0.036 ± 0.002	0.029 ± 0.003	0.052 ± 0.003	0.049 ± 0.006
V_5	R	10.5 ± 1.5	10.7 ± 1.2	16.6 ± 1.9	12.6 ± 2.3
	S	11.3 ± 2.2	8.2 ± 1.9	14.9 ± 2.9	8.2 ± 2.4
	R/S	1.42 ± 0.50	4.48 ± 1.33	2.30 ± 0.90	3.21 ± 0.97
	P.D.T.†	0.023 ± 0.001	0.026 ± 0.001	0.024 ± 0.003	0.026 ± 0.002
V_6	R	9.3 ± 1.4	9.3 ± 1.2	12.7 ± 1.6	9.7 ± 1.8
	S	9.5 ± 1.0	4.3 ± 1.0	9.0 ± 1.4	4.4 ± 2.2
	R/S	1.56 ± 0.38	5.10 ± 1.09	2.88 ± 0.57	4.62 ± 1.23
	P.D.T.†	0.020 ± 0.001	0.026 ± 0.002	0.028 ± 0.002	0.027 ± 0.003

	MEAN VALUES OF MEASUREMENTS IN TOTAL SERIES							
	R_{V_1}	S_{V_1}	$R/S\ V_1$	RV_{3R}	$R/S\ V_{3R}$	S_{V_5}	$R/S\ V_5$	$R_{V_1} + S_{V_5}$
Congenit'l	13.0	3.0	9.8	11.3	9.0	12.1	1.8	26.0
Mitral	4.1	4.7	2.7	3.0	2.3	5.9	5.8	9.7

*All means expressed ± standard error

†Preintrinsicoid deflection time

CORRELATION OF THE ELECTROCARDIOGRAM WITH PRESSURE, FLOW, AND WORK

Table II shows the marked differences present in the mean levels of pressure, flow, and work of the right ventricle in the total group of patients with mitral stenosis and the total group of patients with congenital heart disease. The mean pressure level in congenital heart disease (65.1 mm. Hg) is approximately 50 per cent higher than the 45.2 mm. Hg in mitral stenosis (a significant difference at the 5 per cent level). The mean "flow" level (cardiac index 4.67 L/sq.M./min.) in congenital heart disease is almost double that of mitral stenosis (2.66 L/sq.M./min.). Thus the product of mean right ventricular pressure and flow, namely the right ventricular work, is about three times as great in congenital heart disease (4.04 kg.M./sq.M./min.) as in mitral stenosis (1.41 kg.M./sq.M./min.).

Table II also presents mean levels of pressure, flow, and work for the individual electrocardiographic patterns in mitral stenosis and congenital heart disease. Comparing these mean levels for the patterns of "pure" right ventricular hypertrophy and partial right bundle branch block separately in the two diseases, the same relationship is seen in the individual patterns as in the total tracings in mitral stenosis and in congenital heart disease. A comparison between the "borderline" or normal tracings in the two diseases is not possible because of the small number (three) in congenital heart disease.

With reference to congenital heart disease alone, there were certain differences between the levels of pressure, flow, and work in the patients with electrocardiograms showing "pure" right ventricular hypertrophy and in those with partial right bundle branch block. An unexpected finding was the higher mean flow level in the group with partial right bundle branch block. This difference was probably due to the greater percentage of patients with left-to-right shunts (64 per cent) in partial right bundle branch block. Patients with atrial septal defect and transposed pulmonary veins predominated in this group. In the classic pattern of right ventricular hypertrophy only 39 per cent of the patients had a left-to-right shunt.

In contrast, in mitral stenosis the group of nine with partial right bundle branch block had slightly lower levels of pressure, flow, and work than did those with the classic pattern of right ventricular hypertrophy.

Figure 1 shows the distribution of the three electrocardiographic patterns, the pattern of right ventricular hypertrophy, the pattern of partial right bundle branch block, and the "borderline" or normal electrocardiograms at increasing pressure levels, in mitral stenosis and congenital heart disease.

The distribution of cases at ascending pressure levels in the two diseases is noticeably different. In mitral stenosis a decreasing number of cases appear at the higher pressure levels; but in congenital heart disease, cases are distributed fairly evenly at all pressure levels. For example, 60.9 per cent of cases with congenital heart disease had a mean pressure over 60 mm. Hg; only 18.2 per cent were above 60 mm. Hg in mitral stenosis. This large percentage of cases over 60 mm. Hg in congenital heart disease is responsible for the higher mean pressure in the entire group, as shown in Table I. Most important of all in congenital heart disease, no normal electrocardiogram was found in patients with a mean pressure level over 30 mm. Hg.

TABLE II. MEAN PRESSURE, FLOW, AND WORK OF THE RIGHT VENTRICLE IN CONGENITAL HEART DISEASE AND MITRAL STENOSIS GROUPED ACCORDING TO ELECTROCARDIOGRAPHIC PATTERNS

		CONGENITAL HEART DISEASE				MITRAL STENOSIS			
		RIGHT VENTRICULAR HYPERTROPHY	PARTIAL RIGHT BUNDLE BRANCH BLOCK	† BORDERLINE	TOTAL	RIGHT VENTRICULAR HYPERTROPHY	PARTIAL RIGHT BUNDLE BRANCH BLOCK	BORDERLINE	TOTAL
No. of Cases—		33	28	3	64	19	9	27	55
* Pressure mm. Hg	Mean	73.8	59.3	23	65.1	58.6	47.7	35.0	45.2
	Standard Error	4.2	5.6		3.4	5.9	5.8	2.2	2.4
	Range	35.0–135.0	21.0–123.0	21.0–25.0	21.0–135.0	29.0–129.0	23.0–76.0	19.0–60.0	19.0–129.0
Flow L/sq.M./min.	Mean	4.24	5.36	3.00	4.67	2.67	2.15	2.81	2.66
	Standard Error	0.36	0.51		0.30	0.20	0.20	0.17	0.095
	Range	1.08–10.30	1.47–11.00	2.10–4.80	1.08–11.00	1.35–4.40	1.55–3.62	1.32–4.75	1.32–4.75
Work kg.M./sq.M./min.	Mean	4.38	3.97	0.90	4.04	1.76	1.20	1.25	1.41
	Standard Error	0.45	0.40		0.30	0.17	0.16	0.13	0.09
	Range	1.43–11.92	1.60–9.38	0.66–1.08	0.66–11.92	0.95–3.23	0.56–2.34	0.32–2.99	0.32–3.23

*Mean ventricular systolic ejection pressure.
†No standard error given in this group since there were only three cases.

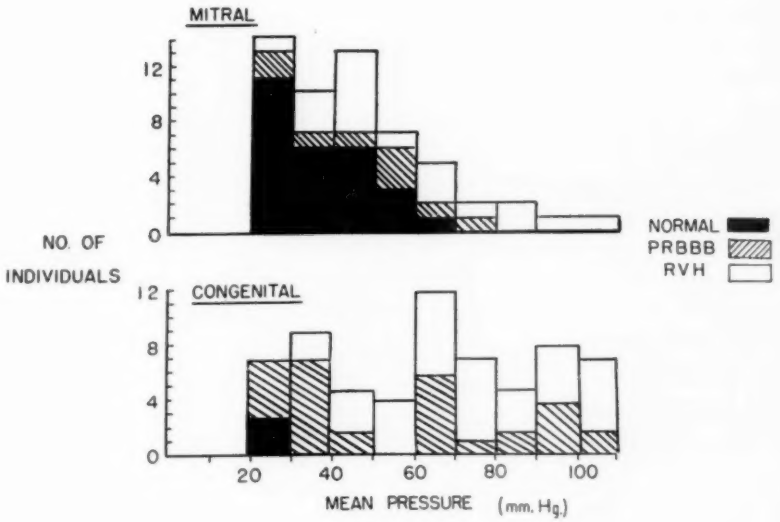

Fig. 1.—Electrocardiographic patterns at increasing right ventricular pressures.

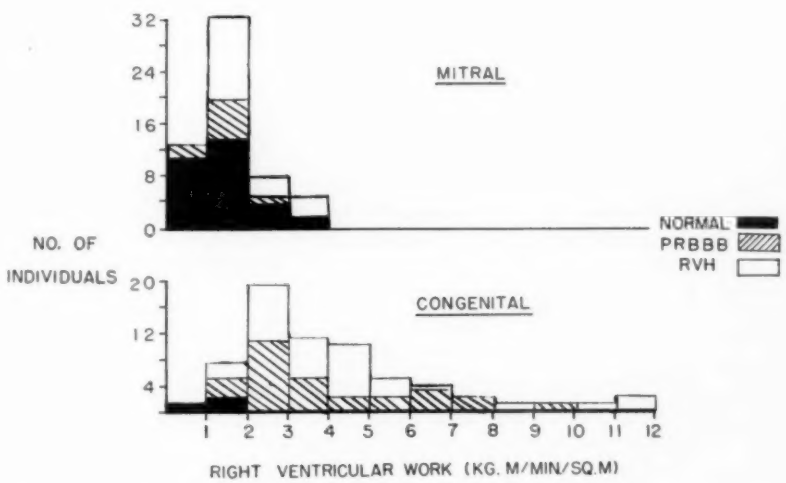

Fig. 2.—Distribution of electrocardiographic patterns with right ventricular work.

In contrast to congenital heart disease, "borderline" or normal tracings appear in mitral stenosis at all pressure levels up to and including 60 mm. Hg. These electrocardiograms constitute 50 per cent of the tracings in mitral stenosis.

A striking finding was the appearance of the partial right bundle branch block pattern at almost all pressure levels in both congenital heart disease and mitral stenosis.

Figure 2 shows the distribution of the three electrocardiographic patterns at increasing work levels. The greater work load in congenital heart disease is obvious; in fact, 85.9 per cent of the patients with congenital heart disease have a right ventricular work over 2 kg. M./min./sq.M.; only 21.8 per cent of the patients with mitral stenosis have a right ventricular work above this figure.

In congenital heart disease, the few "borderline" or normal electrocardiograms occur at normal or only slightly increased work levels. In mitral stenosis, such electrocardiograms occur frequently, at elevated levels of right ventricular work, over 1 kg. M./min./sq.M.

The pattern of partial right bundle branch block again appears at almost all levels of right ventricular work, in both mitral stenosis and congenital heart disease.

The preceding analysis has endeavored to discover the relationship of the three electrocardiographic patterns to right ventricular pressure, flow, and work in mitral stenosis and in congenital heart disease. Next, the individual waves of the electrocardiogram will be compared with right ventricular pressure, flow, and work to estimate the predictive value of any single electrocardiographic abnormality. With this objective in mind, scattergrams were constructed to show the relationship, if any, between (1) the height of R_{V_1}, RV_{3R}, the R/S ratio in V_{3R}, the sum of R_{V_1} and S_{V_5}, the R/S ratio V_5 divided by the R/S ratio V_1, and the preintrinsicoid deflection times in V_1 and V_6 and (2) the right ventricular pressure, flow, and work. Table III shows a selected number of rank correlation coefficients involving pressure and work calculated on the basis of the scattergrams. Correlations involving flow were uniformly poor. In the calculation of the rank correlation coefficients "borderline" or normal electrocardiograms in both mitral stenosis and in congenital heart disease were not included, because the predictive value of only the abnormal electrocardiogram was in question. Electrocardiograms with partial right bundle branch block were included in computing the rank correlation coefficients because, in this series, this pattern showed R/S ratios over the right precordium consistent with right ventricular hypertrophy.

Because the relationship of RV_1 and right ventricular work in mitral stenosis showed the highest rank correlation coefficient, the scattergram of RV_1 versus work in mitral stenosis, and the comparable scattergram in congenital heart disease are presented in Figs. 3 and 4.

In addition, it seemed important to determine whether or not the duration of right ventricular hypertension in each disease was in any way related to the height of right ventricular pressure. In mitral stenosis the total duration of clinical symptoms such as exertional dyspnea was the nearest guide, although an

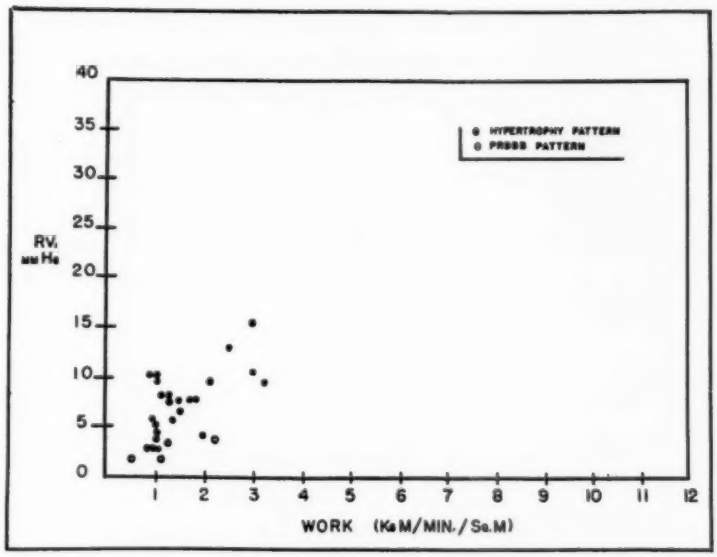

Fig. 3.—Mitral stenosis, height RV_1 versus work.

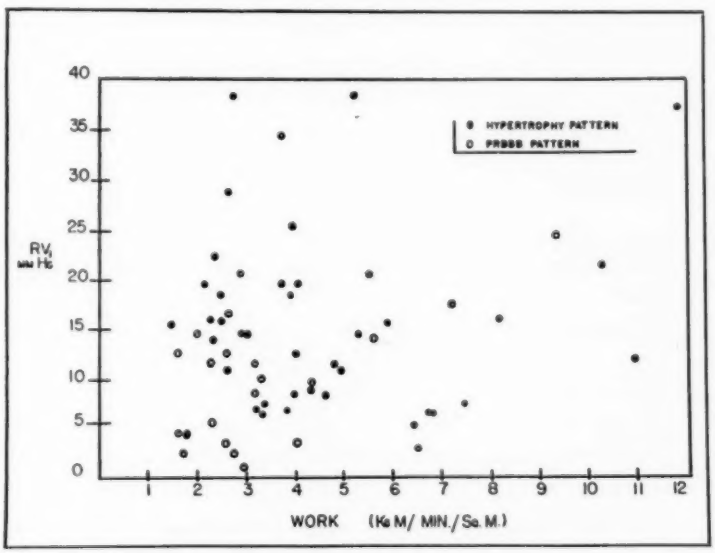

Fig. 4.—Congenital heart disease, height RV_1 versus work.

unreliable one, to an estimate of the onset of elevated pulmonary artery pressure and thus right ventricular hypertension. In congenital heart disease, age was used as an estimate of the duration of right ventricular hypertension. The mean duration of clinical symptoms in mitral stenosis was 25 years; the mean age in congenital heart disease was 19 years. In each disease duration in the individual patient was correlated with levels of right ventricular pressure and work. None of these rank correlation coefficients were significant (all were below plus 0.1).

TABLE III. RELATIONSHIP BETWEEN INDIVIDUAL ELECTROCARDIOGRAPHIC ABNORMALITIES AND RIGHT VENTRICULAR PRESSURE AND WORK IN CONGENITAL HEART DISEASE AND MITRAL STENOSIS AS EXPRESSED BY RANK CORRELATION COEFFICIENTS†

	CONGENITAL HEART DISEASE	MITRAL STENOSIS
Height of RV_1 versus right ventricular work	+ 0.099	+ 0.644*
Height of RV_1 versus right ventricular pressure	+ 0.278*	+ 0.377*
Height of RV_{3R} versus right ventricular work	+ 0.186	+ 0.296*
Height of RV_{3R} versus right ventricular pressure	+ 0.246	+ 0.531*
R/S ratio V_1 versus right ventricular work	− 0.038	+ 0.540*
R/S ratio V_1 versus right ventricular pressure	+ 0.293*	+ 0.532*
R/S ratio V_{3R} versus right ventricular work	+ 0.069	+ 0.606*
R/S ratio in V_{3R} versus right ventricular pressure	+ 0.267*	+ 0.345*
Sum of RV_1 plus SV_5 versus right ventricular work	+ 0.147	+ 0.426*
Sum of RV_1 plus SV_5 versus right ventricular pressure	+ 0.153	+ 0.514*

*Significant at the 5 per cent level.
†Rank correlation coefficients were employed because of the marked skewness of the distributions

DISCUSSION

In comparing electrocardiograms in congenital heart disease and mitral stenosis clear-cut differences have been demonstrated in the height of R and in the size of the R/S ratio over the right ventricle. In both the pattern of right ventricular hypertrophy and partial right bundle branch block (Table I), the height of RV_1, for example, is twice as large in congenital heart disease as in mitral stenosis; the height of RV_{3R} is three times as large.

A similar electrocardiographic comparison has been made by Maurice Campbell,[8] who summarized the works of Goodwin,[9] Woods,[10] and Trounce,[11] in a table comparing the height of R and depth of S in congenital heart disease, mitral stenosis, and cor pulmonale. Campbell's[8] figures are remarkably similar to those of this series. The mean height of his RV_1 in congenital heart disease was 12.5 (this series was 13.0); the mean height of RV_1 in mitral stenosis was (4.7) exactly the same in both series. A particular point is made by Campbell[8] that in mitral stenosis the electrocardiographic abnormalities in V_1 constitute mainly a decrease in the depth of S instead of an increase in the height of R. The figures

in this series provide confirmation. In this connection, a decrease in the depth of S to 2 mm. or less was present in 75 per cent of all abnormal tracings in mitral stenosis.

The assumption has been made that cardiac catheterization can determine the presence of right ventricular hypertrophy. Gordon and Goldberg[12] and Johnson and associates[13] and Cosby and associates[14] have assumed that elevated right ventricular pressure indicates the presence of right ventricular hypertrophy. Cardiac work, the product of pressure and flow, should be more closely related to right ventricular hypertrophy than either right ventricular pressure alone, or flow alone. Lewis and associates[15] have shown a fairly close relationship between pulmonary artery resistance and heart size in mitral stenosis. Certainly it would be reasonable to assume that right ventricular work, as determined by cardiac catheterization, would constitute a valid measure of the degree of hypertrophy of the right ventricle.

It has been demonstrated that in the group of patients with congenital heart disease, with right ventricular hypertrophy confirmed by cardiac catheterization, the electrocardiogram was abnormal in 91 per cent of the cases. In a similar group in mitral stenosis, the electrocardiogram was abnormal in 51 per cent of the cases. In Table II it is pointed out that from a physiologic standpoint in comparing congenital heart disease and mitral stenosis the most extreme differences were in the mean levels of right ventricular work. This was almost three times as great in congenital heart disease as in mitral stenosis. It is logical to assume, then, that some real relationship must be present between the differences in the incidence of abnormal electrocardiograms and in the mean levels of right ventricular work, in the two diseases.

Figures 1 and 2 have shown that a correlation of the three electrocardiographic patterns with either right ventricular pressure or work gives no significant information concerning the relationship of the type of individual electrocardiographic pattern to ascending levels of pressure and work. The pattern of partial right bundle branch block, for example, occurs at almost all levels of right ventricular pressure and work in both diseases. In mitral stenosis borderline or normal electrocardiograms appear at almost all work levels.

Figures 1 and 2 do, however, give valuable information relative to the diagnostic value of the electrocardiogram. In congenital heart disease, elevated right ventricular pressure and/or work is almost always associated with an abnormal electrocardiogram. Conversely, in mitral stenosis, normal electrocardiograms are frequently found in the presence of elevated right ventricular pressure and work.

There are only a few reports by other authors which cover the relationship between electrocardiographic patterns and levels of right ventricular pressure, flow, and work. Recently Watts and associates[16] have reported fourteen patients with mitral stenosis, fourteen patients with congenital heart disease, three with cor pulmonale and three with arteriosclerotic heart disease. The findings of this series compare fairly well with those of Watts and associates[16] when the relationship of $R/S\ V_1$ to right ventricular work is considered. Both Trounce[11] and Lewis and associates[15] have recently correlated the electrocardiographic patterns of

right ventricular hypertrophy with pressure levels in mitral stenosis. Although each series showed a somewhat higher incidence of abnormal electrocardiograms, still normal electrocardiograms occurred at high pressure levels.

In addition to electrocardiographic patterns, individual components of the electrocardiogram were correlated with levels of right ventricular pressure, flow, and work, as shown in Table III. It would seem illogical to believe because of the marked variations of the electrocardiogram with heart position, age, body build, rotation, etc., that any close quantitative relationship could be demonstrated. Nevertheless, it has been noted that the height of RV_1 in congenital heart disease was twice the height of RV_1 in mitral stenosis. In addition the work levels in congenital heart disease are three times as great as those in mitral stenosis. These facts suggest that the height of R, the R/S ratio, etc., in V_1 and V_{3R}, and other diagnostic electrocardiographic abnormalities may be correlated with right ventricular work, pressure, and flow.

Table III shows ten representative rank correlation coefficients relating individual electrocardiographic waves to pressure and work, in both mitral stenosis and congenital heart disease. All of the rank correlation coefficients were significant for mitral stenosis in this table; only three of the rank correlation coefficients in congenital heart disease were significant. In addition, each rank correlation coefficient in mitral stenosis was considerably higher than the comparable figure in congenital heart disease. However, it cannot be assumed that a "significant" rank correlation coefficient present in these groups implies any real predictive value for the particular electrocardiographic abnormality in question.

The striking difference in the correlation of the height of RV_1 and right ventricular work between mitral stenosis (Fig. 3) and congenital heart disease (Fig. 4) is illustrated. The former had a rank correlation coefficient of $+0.64$; the latter had a rank correlation coefficient of $+0.09$. Although a wide scatter is present at high right ventricular work levels in congenital heart disease, a consideration of the relationship at a work level below 4 kg. M./min./sq.M. in each disease also demonstrates the much closer correlation in mitral stenosis. It would seem, then, that in the abnormal electrocardiogram in mitral stenosis, there is some relationship between the increasing height of RV_1 and the gradual development of right ventricular hypertrophy as reflected in the increasing work load. This tendency is not present in the abnormal electrocardiogram in congenital heart disease.

In congenital heart disease, very high levels of right ventricular pressure and flow are present from birth. The normal myocardium is able to hypertrophy and to sustain such high work levels. Intracardiac shunts impose a strain on the right ventricle which is far greater than that present in mitral stenosis, where the ventricular flow is normal or slightly diminished. In congenital heart disease the nature of the abnormality is essentially unchanging and the stress or load on the right ventricle probably does not increase materially with time. But in mitral stenosis there is present a gradual development of increased right ventricular pressure and work. Here the nature of the defect implies a constantly increasing load, with a gradual decrease in the size of the mitral orifice. Right ventricular pressure and work levels rise gradually to heights usually lower than those present

in congenital heart disease. Recurrent rheumatic myocarditis may alter the development of right ventricular hypertrophy. The duration of the disease in mitral stenosis and in congenital heart disease is difficult to compare. In mitral stenosis in particular, the only guide available to estimate the duration of right ventricular hypertension, and thus right ventricular hypertrophy, is the duration of clinical symptoms, an unreliable estimate at best.

The data presented in Figs. 3 and 4 show that the voltage of the abnormal electrocardiogram as expressed in the height of RV_1 is high in congenital heart disease and remains high at ascending levels of work. This behavior of the abnormal electrocardiogram in congenital heart disease reflects the high pressure and heavy work loads sustained by the right ventricle from birth. The congenital lesion is present and fully developed from birth, the heavy load on the right ventricle is constant, and the right ventricle rarely fails. The lesion is not a progressive one, and the original structure of the lesion determines the degree of right ventricular hypertrophy. The electrocardiogram in congenital heart disease is usually abnormal and has marked diagnostic value.

In mitral stenosis, the electrocardiogram is less diagnostic, being frequently normal or borderline in the presence of elevated right ventricular pressure or work. In the abnormal electrocardiogram, however, there is a fairly close relationship between the voltage of the R and S waves in the right precordial leads, as exemplified by the height of RV_1 and ascending levels of work. This is consistent with the developmental nature of the right ventricular hypertrophy due to increasing degrees of stenosis of the mitral valve.

SUMMARY

1. Mean levels of right ventricular pressure, flow, and work, but particularly mean levels of right ventricular work, are considerably higher in congenital heart disease than in mitral stenosis.

2. In congenital heart disease only abnormal electrocardiograms appeared above a mean right ventricular systolic ejection pressure of 30 mm. Hg. In mitral stenosis normal or borderline electrocardiograms appeared frequently up to a mean pressure level of 60 mm. Hg.

3. In congenital heart disease almost all electrocardiograms were abnormal above a right ventricular work load of 1 kg. M./min./sq. M. In mitral stenosis, normal electrocardiograms often occurred at work levels above 1 kg. M./min./sq. M.

4. In both mitral stenosis and congenital heart disease, the pattern of partial right bundle branch block appeared at almost all levels of right ventricular pressure and work, and thus this pattern appeared to be almost as significant as the classic pattern of right ventricular hypertrophy in the detection of right ventricular hypertension and presumptive right ventricular hypertrophy.

5. Gross electrocardiographic differences between congenital heart disease and mitral stenosis were present in all precordial leads; this was most marked in V_{3R} and V_1, where the R wave in congenital heart disease was three to four times as tall as the comparable R wave in mitral stenosis.

6. In congenital heart disease, the electrocardiogram is remarkably accurate (91 per cent of cases) in the detection of right ventricular hypertrophy. In this disease no definite correlation was present between abnormalities of individual waves such as the height of R or R/S ratio over the right precordium and levels of pressure or work.

7. The electrocardiogram in mitral stenosis is less diagnostic (51 per cent of cases) in the detection of right ventricular hypertrophy. But when the electrocardiogram is abnormal, a definite correlation is present between the height of R and R/S ratios over the right precordium and levels of right ventricular pressure and work.

8. These differences in the total electrocardiographic picture suggest fundamental differences in the genesis of right ventricular hypertrophy in the two diseases.

The valuable statistical advice of Dr. John Talbot, and technical assistance of Mrs. Helen Obernolte, Mr. Lucius Collier, Dr. Andrew Farr, and Miss Mary Mayo are acknowledged.

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SPREAD OF ACTIVATION IN THE LEFT VENTRICULAR WALL OF THE DOG. I.

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VERY few experiments have so far been carried out with the aim of a more accurate analysis of the activation of the successive layers of the left ventricular wall. A number of hypotheses concerning the phase of conduction in this part of the heart are more or less generally accepted. The most important is based on the theory of Lewis, extended by Wilson, and applied to the interpretation of many pathologic conditions.

DESCRIPTION OF TECHNIQUE

The instruments used in experiments in this field were either the string galvanometer or a direct-writing pen apparatus, both of which are too slow to allow exact studies of time relationships. We decided to perform a number of experiments and desired to ensure that the results were not obscured by an inadequate technique. The first thing necessary was the construction of a recording apparatus that would fulfill our requirements, which were:

1. The investigator manipulating the electrodes must be able to see the deflections at all times, in order to eliminate the delay otherwise caused in the development of records.
2. There must be at least two leads functioning at all times, so that significant time relation data can be recorded.
3. The time relations within periods as short as 1/2,000 second should be recorded adequately.
4. The nature of the investigation necessitates the use of many leads. Easy access to the leads and quick exchange of electrodes should be possible.
5. The apparatus should be sturdy enough to withstand mechanical shocks during the experiments.

During the early stages of the preliminary experiments it became clear that microelectrodes had to be used. These electrodes have a very high resistance owing to their small diameters. The transitional resistance of a sphere with a radius of a in a continuous medium is $r = \frac{R}{4\pi a.}$ R is the specific resistance of the medium.

If we take a small electrode made from wire 0.1 mm. in diameter, in a medium of 400 ohm-cm., we then have a resistance of approximately 5,000 ohms. In the event of coagulation of blood, greatly increased values may be expected.

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For these reasons the input resistance of the amplifiers had to be as high as possible. This was also needed to maintain the high rejection ratio, which can be seen in Fig. 1. Therefore, the input-impedance in our apparatus is infinitely high, and the object is grounded.

Because of these reasons the apparatus was equipped with two pairs of cathode-ray tubes (Philips D. . 10-6, which are the best tubes in our experience with respect to definition): one pair for the continuous registration and the other pair used for the visual control with a horizontal time basis. In the pair of tubes used for continuous registration, the spot is deflected only by the phenomena being investigated. The pair with the horizontal time basis offers a clear image to the investigator immediately. In this way he can see at once what is happening and can find the best place for his electrodes in a minimum of time.

The cardiographic amplifiers are completely fed by stabilized power supplies. Fluctuation of the mains of as much as 30 volts has no perceptible influence on the recordings. The high tensions and the heater voltages of the amplifiers are kept constant by electronic stabilization. Although there is no need to register phenomena of long duration in these experiments, we have aimed at achieving great accuracy in the reproductions even for the lowest frequencies.

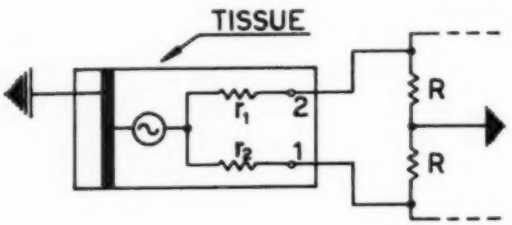


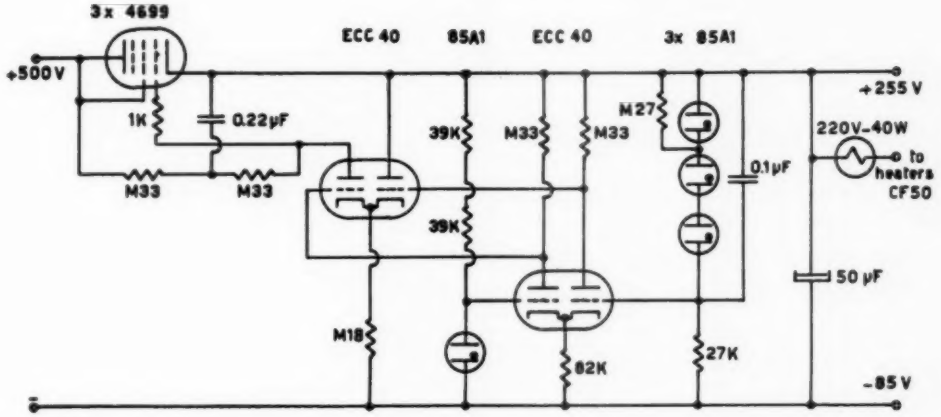
Fig. 1.—One point of the object is grounded, but the object near the electrodes is at a small alternating potential from induction from the mains. This potential is divided into the ratios $\frac{R}{R + r_1}$ and $\frac{R}{R + r_2}$. If r_1 and r_2 differ much, e.g., if one electrode is small (in dimensions or by artifact) then a signal will remain between electrodes 1 and 2.

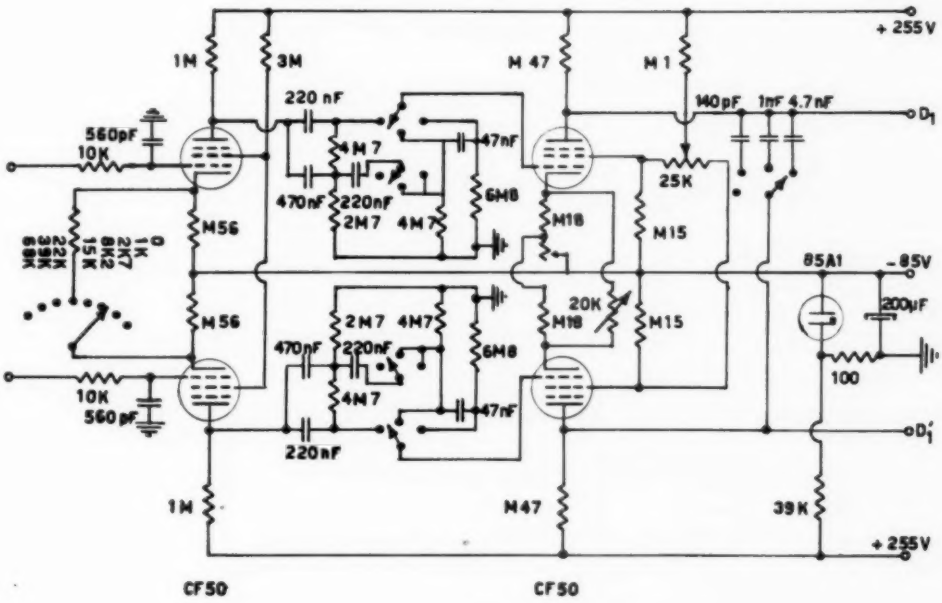
The distortion as well as the blocking time increases steadily with the number of condenser couplings. To keep the distortions and the blocking time down to a minimum, only two amplifier stages were used, both having an extremely high amplification per stage.

The blocking time, which is very closely related to the low frequency response, is always troublesome. To correct this, Dr. F. A. Muller designed the coupling elements, as shown in Fig. 2, combining a large reliability of reproduction with a shorter blocking time than would be the case with an ordinary coupling.

The two channels of the amplifier were designed as a push-pull amplifier with high cathode resistors. Because of these, the two channels possess a large rejection against in-phase signals. This means that signals arriving in parallel at both inputs of a channel are scarcely amplified, while signals which are of a

A.





B.

Fig. 2.—*A* and *B*. The circuit. Only the typical parts of the cardiograph are given in diagrams, the other circuits are just conventional. One of the matters of supreme importance in the construction of such amplifiers is the choice of the first tubes. The Philips CF50 (30V-0.2A used at 0.15 A) proved ideal, especially with regard to the flicker noise. The tubes were selected with respect to their contact potentials and their amplification factor only, since the rejection ratio resulting from this factor is $\frac{\mu_1 - \mu_2}{\mu_1 \cdot \mu_2}$. A tolerance of 1 is taken in the μ_{sg}, which is 40, so that this factor does not impair the rejection to worse degree than 1/1600. When used in the most sensitive manner (cathodes —first stages short-circuited) a difference in electrode potential of 0.1V does not cause a too great asymmetry in anode potentials. On switching towards less sensitivity this tolerance rapidly increases to values which never occur with normal electrodes.

The simple earth stabilization proves entirely successful, even for electro-encephalographic sensitivities. All resistors are of the high stability type.

different sign, and therefore appear between the two grids of the first tubes, are already amplified 400 times in the first stage.

As a result, it is possible, even when working with very high sensitivities, such as a displacement of 8 cm. on the tubes for 0.5 millivolt, to dispense with the Faraday cage. The noise, including the hum, produced at greatest sensitivity, stays far below 10 microvolts root mean square. This method has, however, a certain drawback. The large amplification per stage implies that frequencies above 3,000 cycles/sec. are cut off, which still permits the registration of phenomena lasting 1/20,000 second.

In most recordings an image reduction of 4:1 is applied. The size of the spot is less than 0.4 mm. When the speed of the paper is 20 cm. per second, the resolving power is better than 1/2,000 second. This resolving power can be further increased by increasing the speed of the paper. The amplified signals are put on the vertical plates of two pairs of cathode-ray tubes. The tubes used for photographic purposes are blue and nonpersistent and have an acceleration voltage of 2,000 volts. This causes the spots to be extremely clear, giving excellent recordings on normal registration paper. Even the fastest phenomena, that we met, still give clear traces.

The spots on the tubes used for the photographic records are influenced only by the action potentials. A paper film is moved at right angles to the direction of the deflection of the spot. The image of the spot is brought onto the paper by means of lenses of 10½ or 15 cm. and reduced four times or one and one-half times, respectively, in size.

The paper is driven by a synchronic motor with a possibility of varying the speeds. The speed of the paper is fixed in this way, generally at 10 to 20 cm./sec.

The tubes for visual observation are green and persistent and have a simple horizontal time base, which can be adjusted in steps or continuously. The spot can cross the screen in 5 sec., but for rapid phenomena this can be speeded up to 0.001 sec. The speed of the time base is thus adjusted so that the phenomena can be easily studied on the optical tubes. Of the utmost importance is the way in which the different electrodes required in some experiments are connected to the amplifiers. This must be done with the greatest accuracy since there are sometimes as many as ten electrodes. To this end a plug-in box for ten electrodes and for some ground connections is placed close to the object to be investigated. This box is connected to the apparatus by a cable of approximately 3 meters in length. Selection switches enable the experimentor to bring every required combination of electrodes onto each of the two channels. The sensitivity is adjustable per channel. This adjustment may be made in grades or continuously. The two channels can be calibrated by means of a microswitch. The voltages used vary between one-half and 100 milivolts. The place of the spot on the screen is adjustable with potentiometers. Should it be necessary, the frequencies above a definite value may be cut off. This value may be chosen at 1,200, 150, or 35 cycles/sec. The same applies to undesired low-frequency phenomena, the R.C. time then being 1 or 0.3 sec.

In the experiments the curves registered were without high-frequency cutoffs and with as great a low-frequency cutoff as possible. This could be accomplished without any disadvantage, owing to the short duration of each phenomenon. The advantage of this low-frequency cutoff is that all kinds of movement artifacts are less likely to influence the cardiogram. The recordings of the dog's heart, show no perceptible difference when taken with or without cutoff of the low frequencies. Figure 2 shows the most important parts of the circuit.

Electrode Technique.—After the first few experiments it became clear that new methods had to be devised to investigate the propagation of the activation wave in the left ventricular wall. Theoretically, it seemed improbable that a normal epicardial lead would give sufficient information about the intramural activation processes under the registering electrode.

For this reason Wilson already introduced his "transmural leads." These are records between electrodes at the endocardium and the epicardium, in a line perpendicular to the wall, approximately representing a summation of electrical events taking place in the ventricular wall between these electrodes. But it is clear that even this method does not give exact information on the details of the activation process in the ventricular wall itself. Therefore we decided to study these phenomena by multiple electrodes introduced into the wall.

The lesions caused by the electrodes available at that time proved to be disadvantageous. We surmounted this problem in the following manner. In an ordinary hypodermic needle of 0.9 mm. diameter, holes were drilled in the wall at regular intervals. Wires insulated with a glass capillary were introduced into this needle. These wires were passed through the holes and insulated from the body of the needle with lacquer (Fig. 3). To avoid confusion these small electrodes will be referred to as lead-points. The needles were highly polished so as to make only minimal lesions when introduced in the heart wall. We hope to demonstrate this, as well as the effectiveness of the fixation, in a subsequent paper. This fixation was done with small pieces of "perspex" through which apertures the exact size of the needle had been drilled. The piece of perspex rests with one flat, broad side on the epicardium, so that the needle cannot sink in deeper. This method also prevents pressure injury to the subepicardial tissue. The needle was prevented from working itself out of the wall by its own weight and by fixation of the connecting wires emerging from it.

In another type of needle-electrode two 0.1 mm. wires were brought through each aperture of the needle. In this way two lead-points with a distance of about 0.1 mm. could be made (Fig. 4).

After many trials the technicians succeeded in mounting an increasing number of lead-points in a needle. It was possible to have eleven independent well-insulated lead-points in one needle. The greater majority of the experiments were carried out with an 8-lead-point needle as shown in Fig. 3. All needles had one lead-point at the tip. After we had become familiar with the technique needed in using this type of needle, the form of the complex registered gave us definite information about the region of the wall in which the needle was situated. In

the cases which came to obduction the location arrived at in this way was always confirmed. For measurement at the epicardial surface we used small electrodes with the two lead-points 0.1 mm. apart, insulated with perspex (epicardial differential electrodes).

To enable us to explore a greater part of the epicardial surface of the ventricle, five of these differential surface electrodes were mounted at successive intervals of 2 mm. in a holder. This type of electrode is referred to as the "5-differential surface electrode."

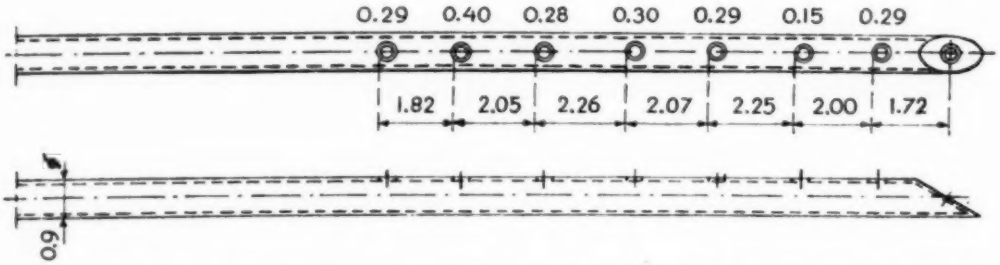


Fig. 3.—"8"-electrode needle. The numbers on the upper row give the diameter of the holes in millimeters. The numbers on the lower row give the distance between the hole in millimeters. The diameter of the needle is 0.9 mm.

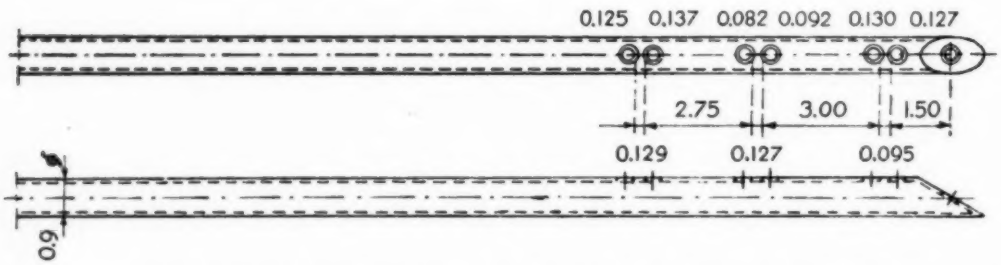


Fig. 4.—Three differential needle-electrode. The numbers on the upper and lower rows have the same significance as in Fig. 3.

If an electric dipole is present somewhere in a continuous medium, the potential at any point is inversely proportional to the square of the distance, when this is large compared with the dipole length, and is also dependent on the orientation of the dipole. The potential difference between two adjacent points is inversely proportional to the third power of their distance from a dipole and proportional to the distance between them. Therefore leads between points adjacent to each other are influenced only by activation of the direct surroundings.

If we have a traveling dipole-front, the potential at each point of the field can be recorded and compared with a distant point. If there is a steep part on the curve we cannot determine the region from which this deflection originates. A differential lead only gives a spike at the moment the discontinuity comes near to the lead-points.

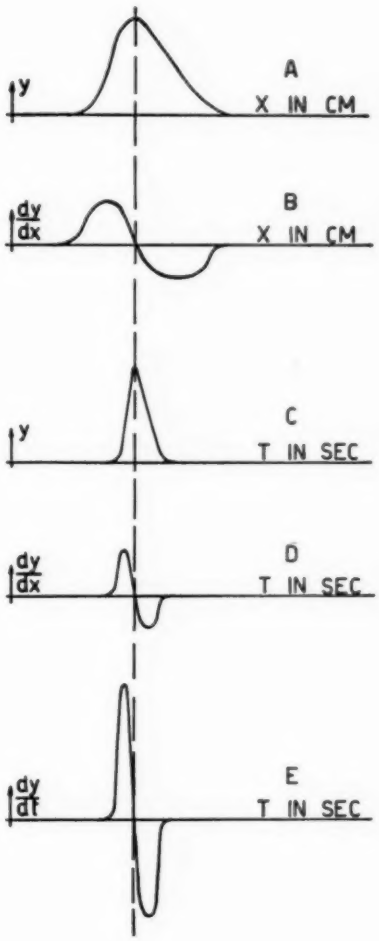


Fig. 5.—See text.

The term "differential lead" is used because of the fact that in certain cases these leads give the space-differentiation of the extrapolated unipolar curve.

For the sake of clarity some elementary facts regarding differential leads are indicated in the following (compare Fig. 5). A clear distinction must be made between differentiation with respect to time and with respect to space.

With our method of analysis we differentiate only with respect to space, which is effectuated by using bipolar leads. Hence if *A* represents the spatial distribution of an action potential on a nerve or a muscle fiber, *B* gives the differentiation of this function (the ordinate is given in arbitrary units):

$$y = f(x), \frac{dy}{dx} = f'(x).$$

On the other hand *C* gives the potential at an arbitrary point as a function of the time when the activation potential is moving along the system (extrapolated unipolar lead). Of course the maximum height of the curve does not change. If the coordinates for 1 sec. and 1 cm. are taken equal, the horizontal stretch varies inversely as the velocity in cm./sec.

Figure 5, *D* now represents the potential, also as a function of the time, taken between two points very close together. The maximum reaches the same height as in *B*, if dx is taken the same. The horizontal stretch, as in *C*, is decreased proportionally to the velocity. If we differentiate *C* with respect to time, the distance in time is v times larger than previously in space-differentiation. Therefore, equivalent differentiation gives maxima that are v times higher Fig. 5, *E*.

We see that space-differentiation always gives the same maximum height independent of the velocity of propagation, while time-differentiation depends linearly on this velocity (a time-differentiation may be performed with the use of an ordinary capacity-resistance filter).

A large number of needles of different kinds were used. For these we use the following terminology. A needle with eight successive lead-points is called an "8-needle." We had four "8-needles," which were identical, including even minute irregularities. We also had an "11-needle" with the 11 lead-points 1 mm. apart.

A needle with five different double lead-points will be called a "5-differential-needle". In Fig. 4 a "3-differential needle" is shown. In each double lead-point the distance between the two points was less than 0.15 mm. We have already mentioned the fact that one separate lead-point was always situated at the tip of the needle. Other needles were made when required and the findings obtained by use of these needles will be discussed in subsequent papers.

REMARKS ON THE REGISTRATION TECHNIQUE

As many different leads as possible are always taken with a needle in one position in order to get the greatest amount of information. For an exact definition of the depth at which the different lead-points were situated an electrode on the leg was taken as a reference electrode. All lead-points were taken successively against this reference electrode. Whenever possible a transmural lead was taken. Its interesting characteristics will be discussed in a subsequent paper. We also recorded an epicardial lead close to the insertion point of the needle.

When a 5-differential needle was used, all combinations of differential leads were made. Also all combinations of one lead-point from each pair of electrodes against a point of another pair were recorded. Only those results were accepted which had no contradictions in the different combinations. Contradictions of this kind were, however, a great exception.

A preliminary report was published elsewhere.[1,2]

SUMMARY

A description is given of the technique adopted for the research of activation processes in the left ventricular wall.

A two-channel cathode-ray tube oscillograph has two tubes for photographic registration and two tubes for continuous visual observation. Simplicity and sturdiness are important.

Electrode needles are described which have a minimal lesion effect and allow the exact positioning of as many as eleven electrodes. These electrodes are situated in one ordinary injection needle.

The technique of registration always consisted in taking as many leads as possible with one needle in one position.

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COMPARISON OF THE DISPLACEMENT, VELOCITY, AND ACCELERATION BALLISTOCARDIOGRAPH IN CORONARY HEART DISEASE

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RECENT publications in the field of ballistocardiography have stressed the high incidence of abnormal records in otherwise clinically normal persons over 50 years of age. Also, the high incidence of normal records in younger patients under 40 years of age with coronary heart disease has been emphasized.[1,2] These findings have raised certain doubts about the usefulness of the ballistocardiograph in clinical medicine. These findings, however, have been with high-frequency ballistic tables of the Starr type which is essentially a displacement measuring device; or direct-body pickups using a photocell or coil-magnet condenser type instrumentation which are also displacement measuring devices or partially integrated velocity curves. To date calibrated instruments have not been used with absolute values in a large series of cases in direct ballistocardiography.

This report will be concerned with absolute values of displacement, velocity, and acceleration measurements in a large group of normal subjects between the ages of 30 and 40 years, and also twenty cases of healed myocardial infarction between the ages of 30 and 40. Since it has been obvious that changes in the ballistocardiographic tracings occur with age, it is desirable to compare normal and abnormal subjects in the same age groups in order to obtain significant comparisons. The instrumentation used in this report is an integrating and differentiating bar-magnet velocity meter which has been calibrated so that simultaneous recording of displacement velocity and acceleration from the same heart beat[3] can be obtained. This technique has certain advantages as it allows for comparisons of acceleration with velocity and displacement and shows the advantages of signal differentiation in order to understand and interpret abnormalities of the displacement curves which may be difficult to detect at the paper speeds used in clinical electrocardiography and ballistocardiography.

METHODS

In order to have a significant comparison between normal and abnormal groups, a sample of fifty normal adults was used between the ages of 30 and 40. No person under the age of thirty was used and no person who had passed his

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fortieth birthday was selected. The clinical material used was largely from people whose physical condition may be important to public safety, such as pilots and control tower operators. There were forty-two men and eight women in this sample. All of the people in the normal group had blood pressures below 150 mm. Hg systolic and 90 diastolic and had no evidence of heart disease or murmurs. All of these people had normal electrocardiograms. Standards have been based on absolute amplitudes, wave ratios, as well as timing of wave peaks.

Displacement and velocity standards are based on absolute measurements of the IJ segment (peak of the I wave to peak of the J wave). Also, the ratio of HI, IJ, and JK segments is expressed as a percentage relationship to each other. Timing of wave peaks is made from the peak of the R wave—Lead I on the electrocardiogram—to the H, I, J, K peaks. Acceleration standards are based on measurement of the aJK segment and from the base line to the aK peak. This has been done because a large percentage of patients with coronary heart disease (especially in the younger age group) show no deviation from normal on the acceleration curves until the J peak has been recorded. The acceleration JK segment represents the acceleration component in time of the motion of the displacement IJ segment. From the base line to the K peak on the acceleration curves represents the acceleration component of the motion from the base line to J peak of the displacement curves, since acceleration is 180 degrees ahead of the displacement curve in phase.

The initial acceleration of the body represented by the aI peak and deceleration as represented by the aJ peak seems to be normal in many cases of coronary disease. The reason for this is obscure, but it may represent the acceleration and deceleration of blood ejected from the right ventricle since the distance of travel in the pulmonary circuit is short and thus may affect the body motion earlier in systole than blood ejected from the left ventricle. Also, the acceleration IJ segment in many normal persons and nearly all coronary patients shows a higher frequency component which has been labeled the I_2 wave[4] and may represent changes in flow due to the bifurcation of the right and left pulmonary arteries. It must be noted, however, that adequate explanation of these findings is still obscure.

All of these records were taken after a rest period of ten minutes with breathing suspended during quiet respiration in the expiratory phase of the respiratory cycle. The legs were suspended from a footrest at such height as to prevent the calves from touching the table. Also, a small segment of elastic stocking was placed between the transducer-platform and the legs in order to control the natural frequency of the platform mass (3 lbs.). The natural frequency of the platform was maintained between 16 and 20 cycles.[5] The recorder used was a Sanborn Poly-Viso four-channel recorder. All studies were done at least two hours after eating.

The recording system of transducer and recorder has been calibrated so that one chart millimeter of amplitude is equal to 0.00020 inch (0.005 mm.) displacement. The velocity trace is calibrated so that one chart millimeter is equal to 0.10 millimeter per second velocity. The acceleration tracing is calibrated so that one chart millimeter of amplitude is equal to 3.0 millimeters per second per

second acceleration. The base line is determined on the acceleration curve by attenuating the signal twenty-five times while the record is being transcribed.

For clinical comparisons, the illustrated charts are used to show the scatter of amplitudes for normal and coronary disease cases. The amplitudes of displacement are measured from the peak of the I wave to the peak of the J wave. The velocity curves have also been measured from the peak of the I wave to the peak of the J wave. (For comparison purposes it is realized that it would be a more proper relationship to measure velocity from the base line to the J peak since velocity is 90 degrees ahead of the displacement curve.) Comparative velocity measurements (from the I peak to the J peak) with base line readings to the J peak show the same overlap between normal individuals and abnormal individuals in this series. However, it may prove more advantageous in the future to measure from the base line and this is being investigated at this time. It is exceedingly difficult to measure from the base line to the J peak on the displacement curves as base line shifts are present because of respiratory changes and the long resistor-condenser time constants involved.

Acceleration is much easier to measure from the base line due to the short resistor-condenser time constants. The acceleration JK is measured as well as the acceleration component from base line to K peak. The illustrated acceleration charts show base line to K peak comparisons only.

NORMAL STANDARDS

Displacement: Fifty Normal Adults (30 to 40 years of age); Mean age, 34 years.
Amplitude IJ = *Mean Value* = 0.0023 inch
Lowest 0.0014 inch (1 case); highest 0.0036 inch (2 cases).
The amplitudes of these fifty normal adults are shown in the chart in Fig. 1.

Wave Ratio Measurements

Mean	Standard Deviation
Percentage HI of IJ	
50	6
Percentage JK of IJ (all cases)	
111	10
Percentage JK of IJ (dIJ 0.0022 inch and over)	
114	9

Timing

	Mean	Standard Deviation
R-K	0.37	0.028
R-J	0.26	0.022
R-I	0.17	0.014
R-H	0.10	0.014

The lowest JK of IJ ratio was one of a 35-year-old woman. This value was 90 per cent (dIJ = 0.0018 inch). The next lowest values were 96 per cent in two cases (dIJ = 0.0020 inch in both cases).

The ratio of JK to IJ is important in coarctation, and thus the standard deviation may be misleading for clinical purposes. All of our cases of coarctation have shown high amplitude IJ segments. When the standards of JK of IJ segments were adjusted to amplitudes (cases with dIJ of 0.0022 inch and over) the mean value of JK of IJ was 114 per cent with a standard deviation of 9 per cent. The lowest percentage of JK of IJ in this group was two cases of 100 per cent. This may prove to be a useful measurement in alterations of the aortic circulation.

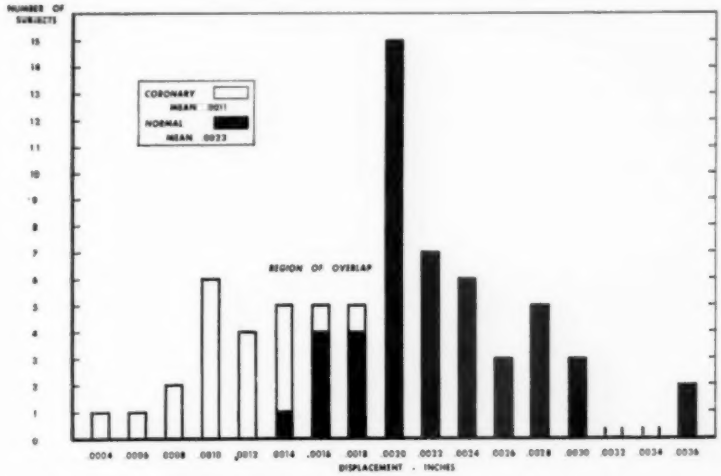


Fig. 1.—Displacement of the body reflected in ballistocardiographic tracings. This chart shows spread of amplitude of displacement IJ segment (tip of I wave to tip of J wave) for fifty normal adults and twenty cases of coronary heart disease between 30 and 40 years of age. Note overlapping between 0.0014 and 0.0018 inch.

Since the mean age of this group of normal persons was 34 years and the mean age of the coronary group was 37, the mean values were also taken between 35 and 40 years of age. The mean age then became 36.5 years and dIJ proved to be 0.0022 inch. The mean values were about the same as when taken for 30 to 40 years. Thus it is probable that the slight age differences between normal persons and patients with coronary disease are of no appreciable significance.

Velocity:

IJ segment = Mean value = 1.7 mm./sec.

Lowest = 1.0 mm./sec.; highest = 2.4 mm./sec.

Wave Ratio Measurements

Mean		Standard Deviation
	Percentage HI of IJ	
53		9
	Percentage JK of IJ	
118		11

Timing

	Mean	Standard Deviation
R-K	0.30	0.024
R-J	0.21	0.017
R-I	0.14	0.010
R-H	0.08	0.014

The lowest HI of IJ value was 40 per cent (1 case) and the highest, 84 per cent (1 case). The lowest JK of IJ value was 92 per cent (1 case); next lowest, 100 per cent (1 case); and the highest, 144 per cent.

It is realized that the velocity IJ segment takes in the I peak of displacement in time relationship, and it may be clinically more accurate to measure from the base line to the peak of the velocity J wave. However, clinical comparisons have shown so little deviation that velocities have been measured from peak to peak.

Acceleration:

JK segment	=	Mean	= 60 mm./sec.^{2}
	=	Standard Deviation	= 11 mm./sec.^{2}
Base line to K peak	=	Mean	= 29 mm./sec.^{2}
	=	Standard Deviation	= 6.0 mm. sec.^{2}

In general there was little similarity between displacement IJ segments and acceleration amplitudes of JK segments. The aJK varied with the sharpness of the displacement IJ slope, but it has not been possible to predict the aJK by simply looking at the displacement curve. Thus, the variation of acceleration amplitudes in all the groups of cases of 0.0020 inch displacement was 24mm./sec.^{2} to 39 mm./sec.^{2} from base line to K peak but slope changes in the displacement curves were of such small order of magnitude that clinical differences were not easy to evaluate. In coronary disease, however, acceleration seems to offer a great clinical advantage as the amplitude from base line to K peak is of a lower order of magnitude and also shows form changes that are easy to see. In all of our coronary cases a definite notching of various degrees has occurred in the acceleration curves which replace the sharp K peak of the normal.

In the evaluation of the low amplitudes in the normal group, six of the eight women in the series were below the mean value of amplitude of 0.0023 inch. One case was 0.0016 inch and three cases were 0.0018 inch. It has been true in our laboratory that cases of hypothyroidism also have low amplitudes so two of the cases of low amplitude (R.T.—age 32 and E.M.—age 37) were re-examined for metabolism studies. These two cases showed no clinical evidence of hypothyroidism (R.T. had a basal metabolic rate of 0 and −9; E.M. had a basal metabolic rate of −15 and −19). It is entirely possible that some of the low amplitudes in normal persons may be due to lower metabolic rates but this needs further investigation.

Also, physical condition seems to play an important part in displacement amplitude. The case with the highest dIJ (.0036 inch) is a 34-year-old pilot who is in excellent physical condition. A recent study of twenty college athletes from a large nearby university all showed displacement IJ amplitudes above 0.0022 inch. The mean value of twenty athletes for displacement IJ was 0.0032 inch.

Body weight may be of significance. In this study, all cases over 160 pounds and under 160 pounds were separated and the mean values of each group were nearly identical. However, mean values of acceleration from base line to K peak

for cases under 140 pounds were 35 mm./sec.^{2} and over 180 pounds were 26 mm./sec.^{2} Mean values of dIJ for both groups were the same, 0.0022 inch.

The relationship of amplitudes of displacement, velocity, and acceleration as compared with cases of coronary disease are illustrated in Figs. 1, 2, and 3.

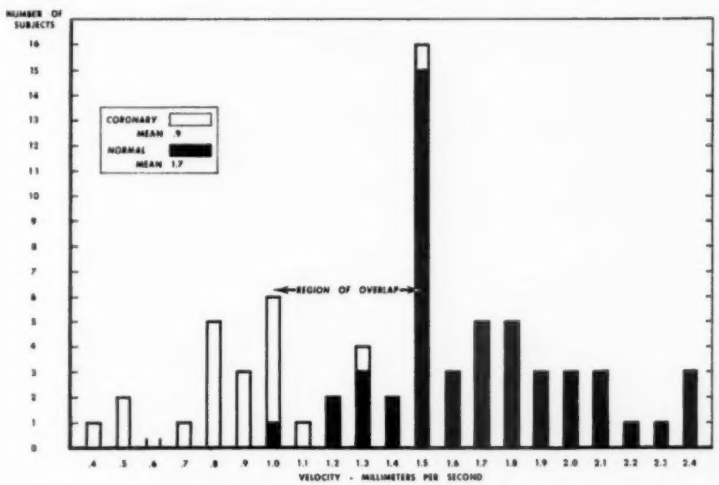


Fig. 2.—Velocity of the body reflected in ballistocardiographic tracings. Spread of velocity measurements of velocity IJ segment (tip of velocity I wave to tip of velocity J wave) in fifty normal adults and twenty cases of coronary heart disease between 30 and 40 years of age.

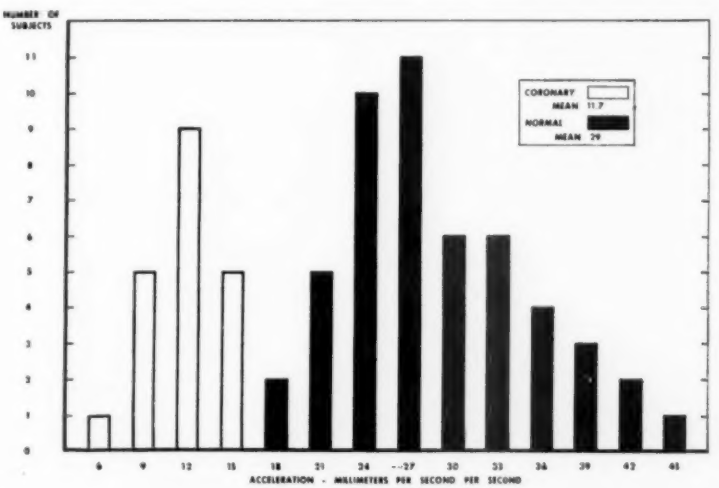


Fig. 3.—Acceleration of the body reflected in ballistocardiographic tracings. Spread of body acceleration measurements from the base line to tip of the acceleration K wave in fifty normals and twenty cases of coronary heart disease between 30 and 40 years of age.

CASE ILLUSTRATIONS

CASE 1.—A normal 35-year-old pilot showing relationship of displacement, velocity, and acceleration while breathing and with suspended respiration. This case is very close to the mean values of the three types of measurement (Fig. 4).

CASE 2.—A normal 32-year-old woman, weight 140 pounds. No evidence of heart disease. This patient had been to see a physician three years ago with a complaint of fatigue. Basal metabolic rate was low normal. At present has no complaints but leads a sedentary life. Displacement, velocity, and acceleration all show low amplitudes and are well below mean values.

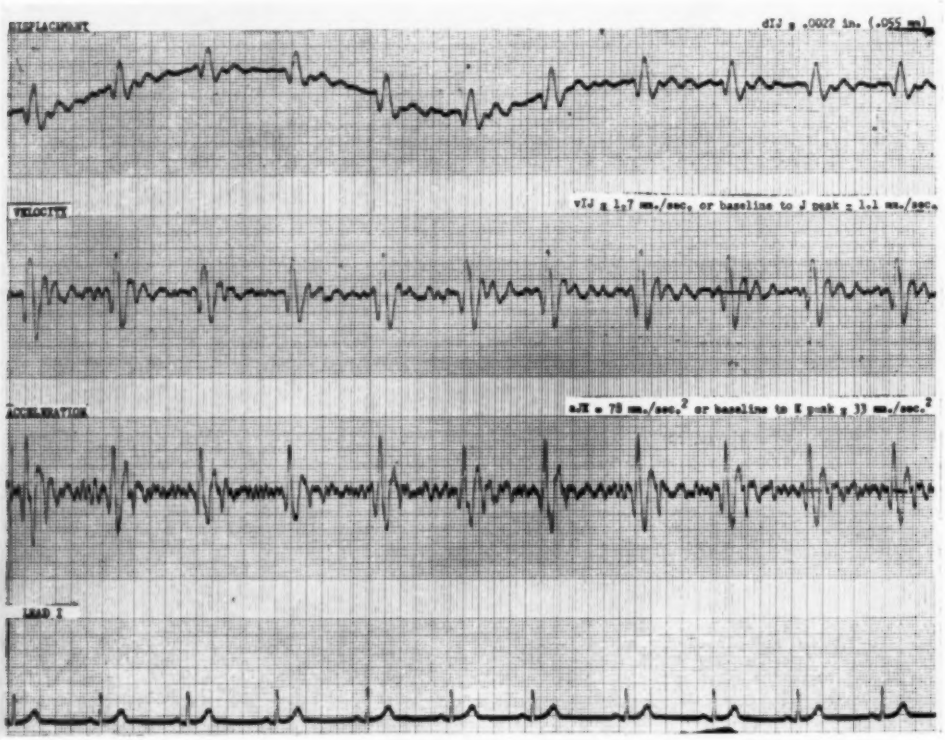


Fig. 4.—Simultaneous calibrated recording of displacement, velocity, and acceleration from a 35-year-old normal man, while breathing and with suspended respiration.

No clinical symptoms of hypothyroidism. Basal metabolic studies taken a few weeks after the ballistic trace showed values of 0 and −9. Blood pressure, 96/60 mm. Hg (Fig. 5*A*).

CASE 3.—A 37-year-old man shows the lowest displacement IJ amplitude of the series of 50 normal individuals in the displacement and velocity curves. No history of any difficulty with health. Blood pressure, 122/82 mm. Hg. Basal metabolic rate, −15 and −19* (Fig. 5,*B*).

CASE 4.—A 31-year-old man, weight 235 pounds. This case had no complaints and seemed to be in excellent health. However, this is the only low amplitude normal that showed form abnormality. The HI of IJ velocity curve equals 85 per cent; JK of IJ equals 92 per cent. Also, the acceleration base line to K peak was the lowest in the normal group, 18 mm./sec.² (Fig. 5,*C*).

*The apparent discrepancy of velocity IJ segment of 0.9 mm./sec. in the photograph of this case, and the lowest amplitude velocity IJ of the chart in Fig. 2 is due to the fact that the average of five complexes was slightly higher than the section used for photography.

CASE 5.—A 34-year-old man, pilot for a high government official. Excellent physical condition, weight 147 pounds. This was the highest displacement amplitude in the series of normal cases. Blood pressure, 118/70 mm. Hg (Fig. 5,*D*).

CORONARY HEART DISEASE

Twenty cases—Mean age, 37

Displacement IJ = *Mean Value* = .0011 inch

Lowest 0.0004 inch (1 case); highest 0.0018 inch (1 case)

Wave Ratio Measurements

Mean		Standard Deviation
	Percentage HI of IJ	
71		24.5
	Percentage JK of IJ	
130		28.7

Timing

	Mean	Standard Deviation
R-K	0.38	0.022
R-J	0.27	0.02
R-I	0.17	0.03
R-H	0.10	0.02

Velocity Amplitude IJ = *Mean Value* 0.9 mm./sec.

Lowest = 0.4 mm./sec. (1 case); highest = 1.5 mm./sec. (1 case)

Wave Ratio Measurements

Mean		Standard Deviation
	Percentage HI of IJ	
79		20.5
	Percentage JK of IJ	
115		25.98

Timing

	Mean	Standard Deviation
R-K	0.33	0.024
R-J	0.22	0.026
R-I	0.15	0.024
R-H	0.08	0.017

Acceleration: JK segment = Mean = 33.7 mm./sec.^{2}

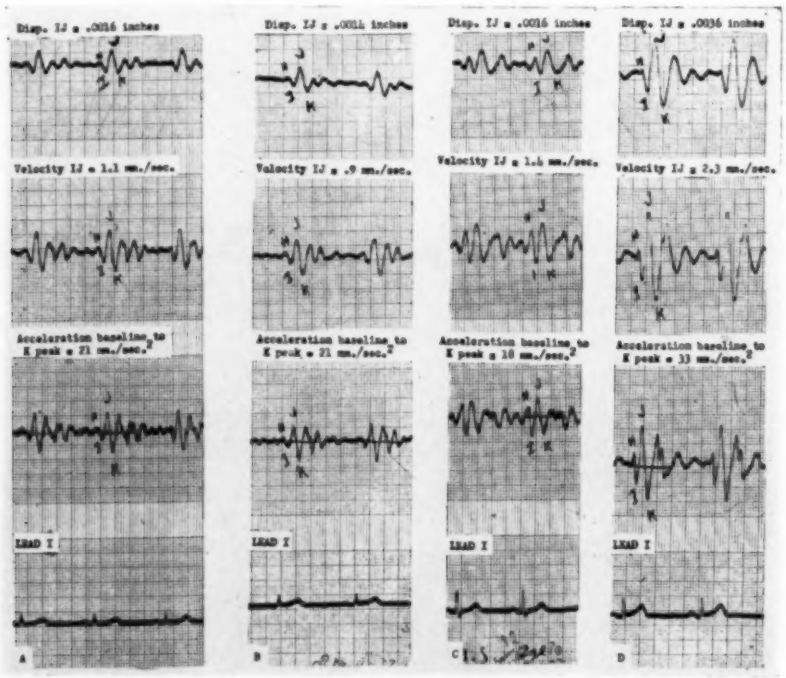
= Standard Deviation = 7 mm./sec.^{2}

Base line to K peak = Mean = 11.7 mm./sec.^{2}

= Standard Deviation = 2.5 mm./sec.^{2}

The amplitudes of displacement, velocity, and acceleration in these twenty cases are illustrated in Figs. 1, 2, and 3 to show comparison and overlapping. If the acceleration curves are measured from base line to K peak, there is a much shorter cutoff point between normal and abnormal. Thus, three cases of the coronary group were read at 15 mm./sec.^{2} All of these cases showed a higher

frequency notching, and this may be an important diagnostic point. If a sharp line in body acceleration with form abnormality can be demonstrated in a much larger series of cases between normal and abnormal, the measurement of body acceleration may prove to be an improvement in method in clinical medicine. Cases of neurocirculatory asthenia and anxiety states have shown high amplitude acceleration curves in our experience and the study of neuropsychiatric disorders may prove fruitful since the acceleration curves seem to be a sensitive index to overstimulation of the cardiac accelerator mechanisms.[6]



A. *B.* *C.* *D.*

Fig. 5.—Tracings taken from three low-amplitude normal persons and the highest amplitude normal person from fifty normal adults between 30 and 40 years of age.

(*A*) A 32-year-old woman, basal metabolic rate, 0 and −9, weight, 140 pounds;
(*B*) A 37-year-old man, basal metabolic rate, −9 and −15, weight, 157 pounds;
(*C*) A 31-year-old man, shows lowest amplitude acceleration K wave, weight, 235 pounds;
(*D*) A 34-year-old man, highest amplitude displacement curve of the normal group of fifty cases, weight, 147 pounds.

CASE 6.—A 31-year-old soldier who had an attack of substernal chest pain with radiation to the left arm. An electrocardiogram showed typical changes of an anteroseptal infarct. The tracing is illustrated in Fig. 6 and was taken after the patient was ambulatory and infarction was healed. No angina, but electrocardiogram shows QS pattern and T-wave changes measured from V_2 to V_4. Note the base line illustration shown on the acceleration curve. This is done by rapidly attenuating the signal twenty-five times. Note the pattern of notching of acceleration K with another notch on the aKL segment. Also, the displacement curves show low amplitude, but form abnormality is extremely difficult to see if the displacement curves only are recorded. This case was the youngest in our coronary heart disease group.

CASE 7.—A 33-year-old soldier. Typical history of acute myocardial infarct, anteroseptal with proved electrocardiograms. Residual QS patterns in V_1 to V_2. Blood pressure, 128/70 mm. Hg. Tracing taken when patient was ambulatory, several weeks after healing had taken place. Note the marked abnormality of wave-form and wave-ratios. The acceleration curves show loss of sharp K wave peaks and are replaced by high amplitude notch. This is manifested on the displacement J wave as rounding and flat tops (Fig. 7).

CASE 8.—A 38-year-old man. History of anginal pain, retrosternal, on exertion, lasting two weeks. Severe steady substernal pain lasting for nine hours. Electrocardiogram showed typical pattern of acute posterior myocardial infarction. Ballistocardiogram was taken two months later after healing and patient was ambulatory. Blood pressure 116/72 mm. Hg. Recovery was

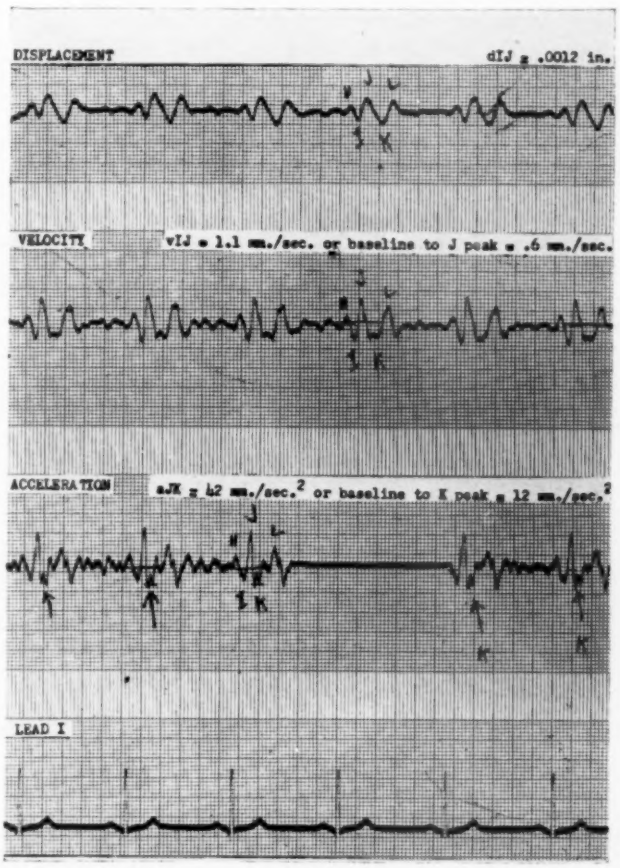


Fig. 6.—Healed myocardial infarct. Ballistic tracings of the youngest, age 31, of the series of twenty coronary cases. Note the base line on the acceleration curves and abnormal components from acceleration base line to tip of the L wave. Case No. 6.

uneventful. This case is illustrated because the amplitudes are the lowest values found in the twenty cases of coronary heart disease (Fig. 8).

CASE 9.—A 37-year-old man with history of sudden onset of severe substernal chest pain lasting about one-half hour following moderate exertion. Pain subsided but the patient was hospitalized. Electrocardiogram taken immediately was normal but several tracings over a period of three weeks showed RS-T segment and T-wave changes with no Q waves. During and following the healing, Lead aV_L showed an inverted T wave with slurring and notching of the downstroke of the R wave. V_1 and V_2 showed low amplitude S waves. Diagnosis was made of myocardial infarction.

The ballistocardiogram was taken six months after healing. This tracing is illustrated because it is the most normal tracing that we have seen in our laboratory with known coronary heart disease. The patient is symptom free and displacement and velocity curves appear normal. The acceleration curves, however, show usual patterns of notched K peak and slope changes to peak of the acceleration L wave (Fig. 9).

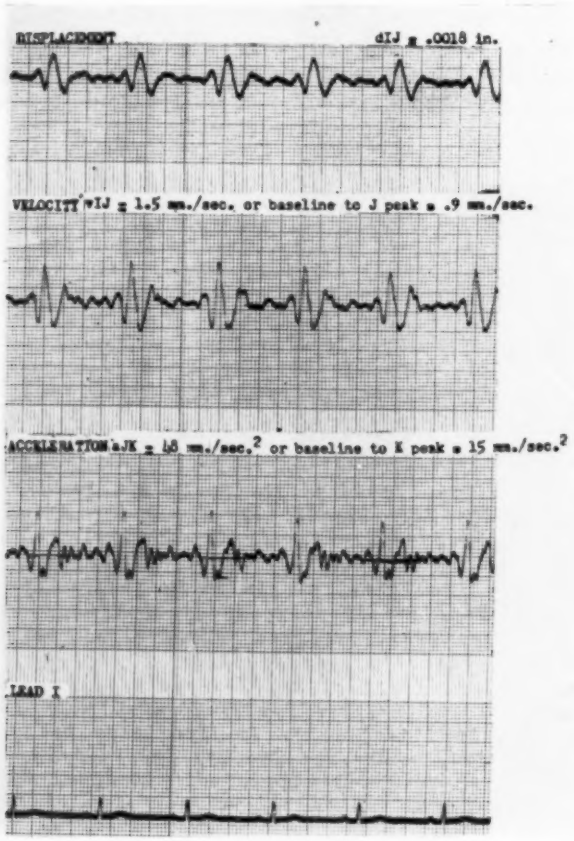


Fig. 7.

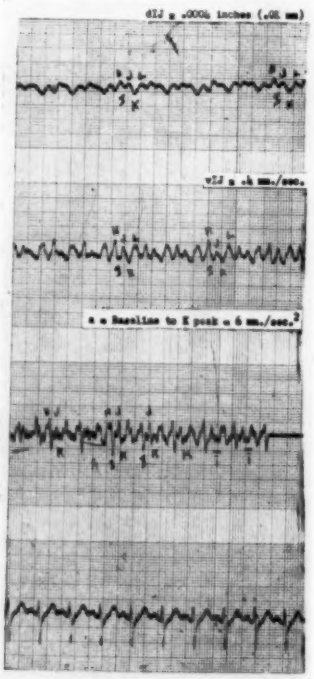


Fig. 8.

Fig. 7.—Healed myocardial infarct. Ballistic tracing of a young patient, age 33, with coronary heart disease. Note the form abnormality on all components. The rounding and flattening of the displacement J tip is seen on the acceleration curve as a higher amplitude notching. Case No. 7.

Fig. 8.—Suspended respiration. Ballistic tracing of a 38-year-old man with coronary heart disease. This tracing shows the lowest amplitudes of the group of 20 cases. Case No. 8.

DISCUSSION

It is impossible at this stage of the development of ballistocardiographic techniques to be certain of the exact value of calibrated instrumentation. It is certain, however, that calibration of instrumentation will be of no value unless the total system can consist of calibrated-instruments as well as techniques for using them. It is still uncertain whether the use of a heavy mass on the legs can be tolerated even when a segment of elastic stocking is used to raise the frequency of the platform. It is quite probable that with the techniques used in this paper clinically useful data are possible. However, the mass placed on the legs with its natural frequency and damping will need much further investigation to be certain

of the deviations from the response curve of a single degree of freedom system. It would also seem appropriate to mention that studies of body damping will be of limited value until it can be certain that the transducer mass on the legs is not introducing errors of motion measurements. When the effects of a second degree of freedom of transducer-mass on the legs can be studied accurately, studies of

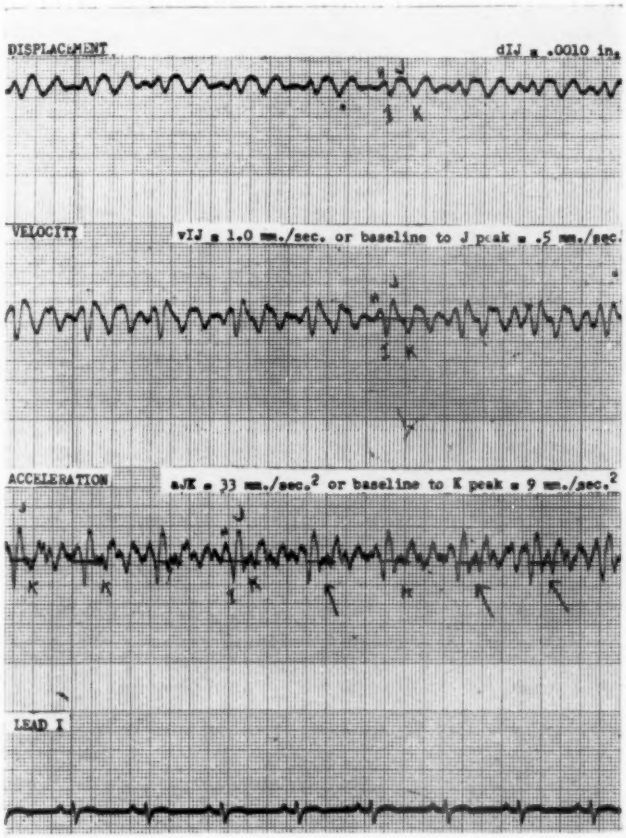


Fig. 9.—Ballistic tracing of B. M., a 37-year-old man, showing the highest amplitude and most normal appearing tracing of the group of 20 cases of coronary heart disease. Case No. 9.

body damping should be fruitful as the errors of amplitudes and distortion produced by the body may be more sharply defined. The application of normal standards will have to await further analytical studies of the body before a clinically sound technique can be of wide application. Normal standards published in this paper are standards only for the technique used to develop them.

SUMMARY AND CONCLUSIONS

1. The results of simultaneous calibrated recording of displacement, velocity, and acceleration components of body motion have been presented in fifty normal adults and twenty cases of proved coronary heart disease between the ages of 30 and 40 years.

2. The demonstration of abnormality of form and amplitude in coronary type heart disease is more pronounced and more definitive in pattern on the acceleration curves than in either the displacement or the velocity.

3. The measurement of body acceleration should be attempted in ballistocardiography.

Grateful acknowledgment is made to the Cardiology Department, Walter Reed Hospital and the Medical Department, Fort Belvoir Hospital, for furnishing some of the clinical cases used in this study.

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BALLISTOCARDIOGRAPHY WITH ELIMINATION OF THE INFLUENCE OF THE VIBRATION PROPERTIES OF THE BODY

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THE ballistocardiogram (BCG) is a record of the oscillatory body motion which occurs with every heart beat and is therefore attributed to forces produced by the heart action. Usually the component of deflection or velocity parallel to the longitudinal body-axis is recorded when the body is lying: (a) free on a rigid surface (Dock method)[1] or (b) fixed on an elastically suspended table (Starr method).[2]

In each case a force produces the body motion. This force alone is directly connected with the heart action whereas the motion of the body depends on the mechanical system between force and motion as well as on the force. The mechanical system consists of the system of the table and that of the body. The latter can be separated into the "external network" and the "internal network" (see Theory).

In the present paper a method is presented (based on the Starr method) which eliminates the influence of the mechanical system of the table and of the external body mechanical network. The record of the table motion is then proportional to the force, F_B, at the "input" of the external body mechanical network.

THEORY

The Recording of F_B.—The complete mechanical system in the ballistocardiographic recording consists of the body system (the masses of the body parts and the elasticities and dampings which connect these parts to each other and to the surface on which the body lies) and the table system (its mass, elasticity, and damping of its suspension). The body mechanical network can be separated into two parts: (a) an "external network" formed by the masses of the external body parts (head, legs, arms, trunk) and the elasticities and dampings which connect these parts to each other and to the surface on which the body lies; (b) an "internal network" which may, as a first approximation, be assumed to be formed by the masses of heart and liver and the elasticities and dampings which connect them to each other and to the skeleton which may be considered as the "input" of the external network.

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The division of the body mechanical network into these two parts is useful because: (a) the coupling between the two parts is weak (the impedances of the internal network are small in comparison to the impedance of the total body mass) and the combined response of both is therefore obtained by the product of the responses of each; (b) the external network can be determined by relatively simple measurements.

It is possible to determine the external body network in the frequency range of 1 to 15 cps. by measuring the body velocity caused by sinusoidal forces applied to the body.[4] The application of these forces has to produce the same "pattern of motion" of the body as the one produced by the heart action. It is shown by the similarity of ballistocardiograms recorded from various points of the body (using the Dock method) that all external body parts move with approximately the same amplitude and phase in response to the heart action.

The same pattern of motion is obtained when the body is placed on a shake-table oscillating parallel to the longitudinal axis of the body.*

By measuring the amplitude of the body and of the table at various frequencies it is found that the external body network can be closely represented by a simple oscillator formed by the "total body mass," M_B, and the compliance, E_B, and the damping resistance, R_B, of the external tissues. The system has a resonance frequency, $F_B = \frac{1}{2\pi}\sqrt{\frac{1}{M_B E_B}}$, of about 3 cps. and a Q_B† of about 3 when the body lies free on its support.[4] When the body is clamped between plates (connected with the support) at the feet and the shoulders it has a resonance frequency of about 9 cps. and a Q_B of about 2.5. These values vary within relatively narrow limits among subjects of normal body build.

Figure 1,*A* shows the mechanical circuit of the body (M_B, E_B, R_B), on the ballistocardiographic table (M_T, E_T, R_T).‡ The equivalent electrical circuit,[5,6] shown in Fig. 1,*B* was used to determine by electrical measurements the response of the mechanical system.

The record of any physical quantity, P, describing the table motion can be proportional to the force, F_B, acting upon the body only when the ratio P/F_B as a function of frequency is constant in the frequency range of interest. Measurements and calculations show (Fig. 1,*C*) that in our system, in case of appropriate damping and in case of harmonic oscillations, the ratio:

$$\frac{\text{velocity, } V_T}{\text{force, } F_B}$$

(a) increases in frequency range I (0 to f_1) essentially in proportion to the frequency, f, i.e., the deflection of the table is proportional to the force (velocity = $2\pi f \times$ deflection),

*First experiments in this direction were performed in 1949 together with K. R. Reissmann in the School of Aviation Medicine, Randolph Field, Texas.

†"Q" indicates the rate of increase, caused by resonance, of the amplitudes of an oscillating system. Q is defined by the ratio: mass or spring reactance at resonance frequency to damping resistance.

‡W. K. Harrison, Jr. (Johns Hopkins Hospital) derived the same mechanical circuit independently (personal communication to the author).

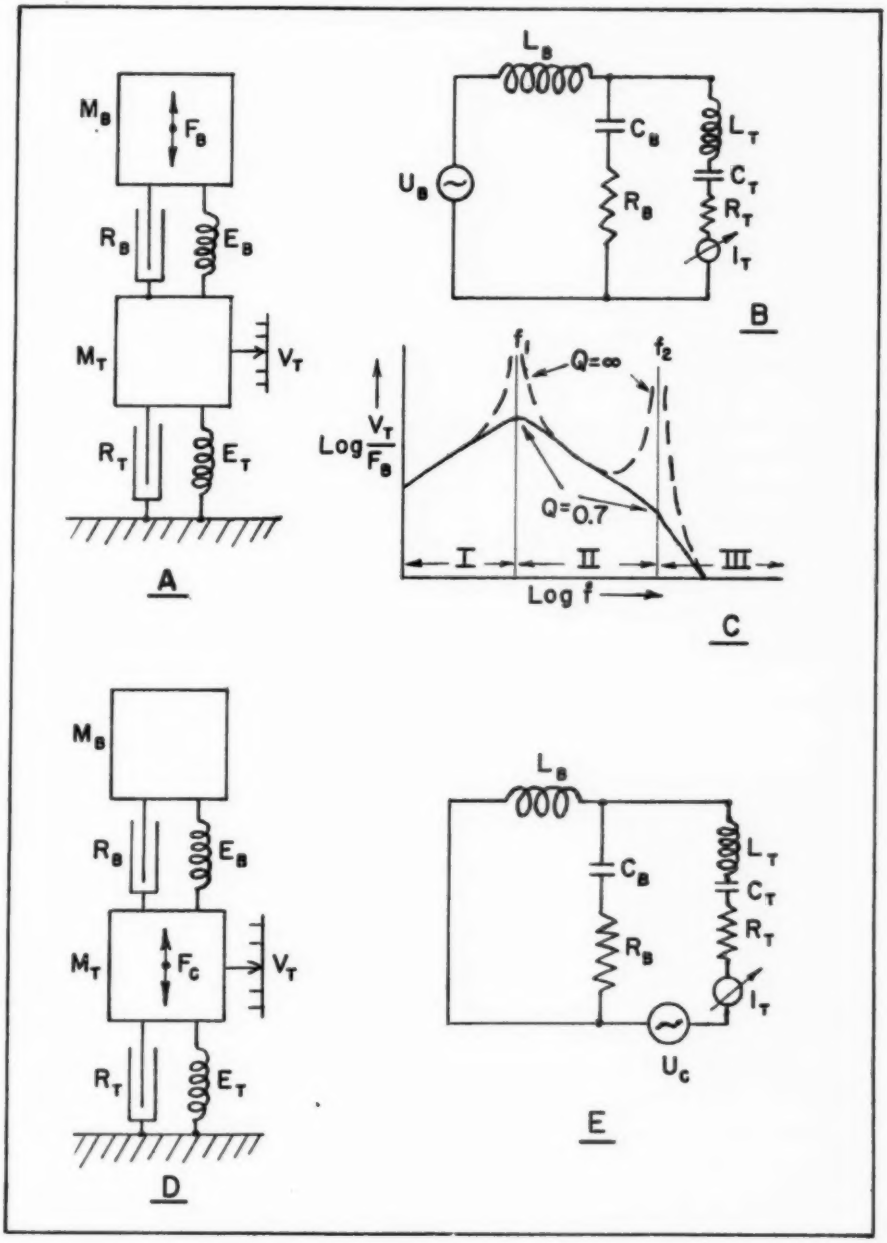


Fig. 1.—*A*. Mechanical circuit of the body lying on a table—ballistocardiograph (for the BCG recording). *B*. Equivalent electrical circuit of *A*, *L* corresponds to *M*, *E* corresponds to *C*, *R* corresponds to *R*, *F* corresponds to *U*, *V* corresponds to *I*. *C*. Frequency response characteristic of the system shown in *A*. *D*. Mechanical circuit of the body and of the table for calibration by means of a force applied upon the table. *E*. Equivalent electrical circuit of *D*.

(b) decreases in frequency range II (f_1 to f_2) essentially in proportion to 1/f, i.e., the acceleration of the table is proportional to the force (acceleration = $(2\pi f)^2 \times$ deflection),

(c) decreases in frequency range III (f_2 to ∞) essentially in proportion to $1/f$.[3]

$$f_1 \sim \frac{1}{2\pi}\sqrt{\frac{1}{M_B E_T}} \text{ and } f_2 \sim \frac{1}{2\pi}\sqrt{\frac{1}{M_T E_B}} \text{ when } E_T \gg E_B \text{ and } M_B \gg M_T.$$

With decreasing compliance E_T of the table suspension, f_1 increases up to $f_1 = \frac{1}{2\pi}\sqrt{\frac{1}{M_B E_B}} = f_B$, while with increasing table mass M_T, f_2 can decrease down to f_B. The values at f_1 and at f_2 which are infinite when there are no damping resistances within the system (dashed curve; $Q_{f1} = Q_{f2} = \infty$) can be diminished to the values of the solid curve by proper damping of the system ($Q_{f1} = Q_{f2} = 0.7$). The damping, R_T of the table affects mainly the value of Q_{f1} while the damping, R_B, of the body tissue affects mainly the value of Q_{f2} (when $M_T \ll M_B$). The proper damping of the table ($Q_{f1} = 0.7$) can be achieved by using a damping device connected with the table, while the proper damping of f_2 can be obtained by making the mass of the table such that $Q_{f2} = \frac{2\pi f_2 M_T}{R_B} = 0.7$. In order that the record of the table motion be proportional to the force, F_B, the ballistocardiograph must be designed so that the entire frequency range of interest for the ballistocardiogram (i.e., from f′ to f″) is either in range I or in range II or in range III. In the first case, f_1 must be $> f''$ and the deflection of the table must be recorded. In the second case, f_1 must be $< f'$ and f_2 must be $> f''$ and the acceleration of the table must be recorded. In the third case, f_2 must be $< f'$ and the second time derivative of the acceleration must be recorded. In all other situations where f_1 or f_2 (or both) are within the frequency range of interest, a record proportional to the force cannot be obtained by recording simply the deflection or one of its time derivatives. This is the case for almost all ballistocardiographs now in use.

By a change of the mechanical table constants, f_1 cannot be made greater* and f_2 cannot be made smaller than f_B. To produce case I, f_B must be made $> f''$ (by the fixation of the body to the table) and the mass of the table and its compliance must be small. To produce case II it must be made: $f_B/f'' = \sqrt{M_T/M_B}$ (by a fixation of the body to the table or by changing the value of M_T/M_B); and the compliance of the table must be large and its mass small. To produce case III, f_B must be made $< f'$ (e.g., by means of a very soft rubber mattress between body and table) and mass and compliance of the table must be very large. The

*I am indebted to Dr. S. H. Talbot, Johns Hopkins Hospital, for this hint.

usual "high frequency" table approaches case I, the "low frequency" table case II. One can show that the sensitivity of the system is greatest in case II which can also be accomplished in practice most easily because it requires the most simple body fixation. Hence, this case alone will be considered in the following discussion. If we want to record F_B in the frequency range $f' = 1$ cps. to $f'' = 15$ cps., which was considered sufficient, the body must be clamped to the table (so that $f_B \sim 9$ cps.) and M_T must be made $< M_B/5$ to obtain $f_2 > 15$ cps. Fortunately, R_B has such a value that with this table mass the correct damping at f_2 is also obtained. Furthermore, f_1 must be made < 1 cps. by a large compliance of the table suspension.

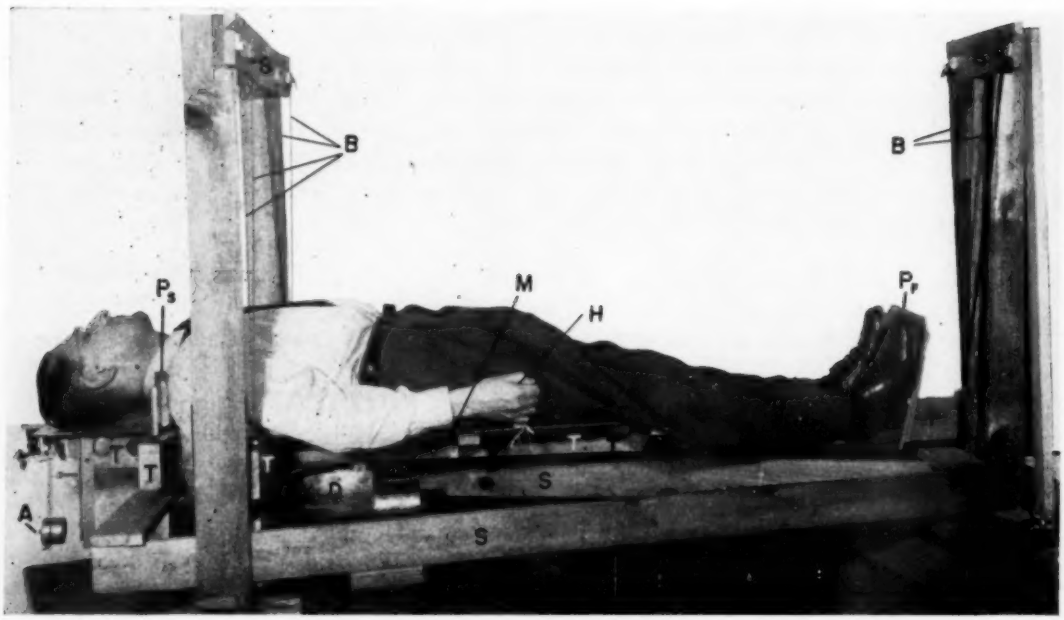
Calibration of the F_B Record.—For calibration of the F_B record one should apply a known force, F_C, to the total body mass, M_B. This is difficult because the body mass is only accessible through the elasticity of the external tissues and the validity of the concept of a total body mass depends on the way the force is applied. In our system one can, however, under certain conditions apply to the table a calibration force which is equivalent to a force applied to the body mass. Figure 1,*D* shows the mechanical circuit and Figure 1,*E* its equivalent electrical circuit for this kind of calibration. The voltage, U_C, is equivalent to the calibration force, F_C, applied upon M_T. In the recording of F_B (case II) there is practically no relative motion between body and table. For calibration the same pattern of motion must be produced. The frequency, f_C, of the (preferably sinusoidal) calibration force must therefore be below f_B where $1/2\pi f E_B \ll 2\pi f M_B$ and it must be in the flat range of the frequency response characteristic of the system, i.e., above f_1. In order to make the calibration independent of the mechanical constants of the subject, one may choose as the calibration frequency the geometric mean of f_1 and f_B: $f_C \sim \sqrt{f_1 \times f_B}$. The reaction force of an oscillating mass M_P (mass loaded pendulum)[3] connected to the table can most conveniently be used for calibration. This force is:

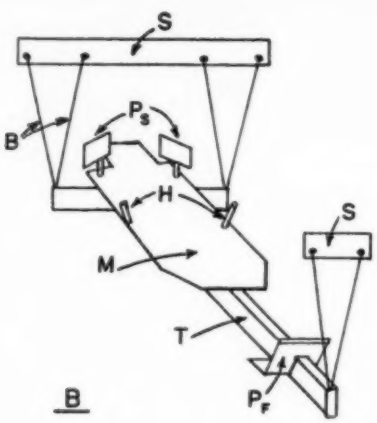
$$F_C = M_P \, a \, \omega_C^2$$

(a = amplitude of deflection of M_P; $\omega_C = 2\pi f_C$). In order to obtain a record of F_C, undistorted by the ballistocardiogram which cannot be "switched off" during calibration, the frequency response of the recording system can be cut off above f_C when the sensitivity of the system for f_C is not changed thereby. By means of a contact, operated by the pendulum, a voltage pulse can be produced and recorded which indicates the direction of the force.

Table Ballistocardiograph for the Recording of F_B.—Figure 2 shows a photograph and a schematic diagram of a table ballistocardiograph designed according to the above considerations for the recording of F_B in the frequency range of 1 to 15 cps. The table plate is formed by a light wooden structure, *T*, covered by a "Masonite" plate, *M*. The subject is clamped between plates; two at the shoulders, P_S (adjustable according to the shoulder angle), and the foot plate, P_F (adjustable according to the size of the subject). The hands grip two insulated metal handles, *H*, which are used at the same time for electrocardiograph electrodes.

A.





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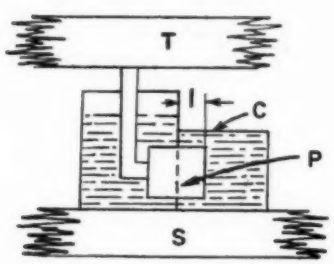

C.

Fig. 2.—*A*. Table ballistocardiograph with subject. *B*. Schematic presentation of the ballistocardiograph. *C*. Schematic presentation of the damping, *D*, in Fig. 2, *A*.

At three points the table is suspended in the supporting structure, *S*, by pairs of steel bands, *B*, arranged in the form of a V. The bands are 70 cm. long. The natural frequency, f_T, of the table (which forms a pendulum) is therefore 0.6 cps. loaded or not loaded with the subject ($f_T = f_1$). The V-arrangement of the bands allows the table to move only parallel to its longitudinal axis. The mass of the table is 10^4 grams. In case of a subject weighing 8×10^4 grams, f_2 is therefore:

$$f_2 = f_B\sqrt{M_B/M_T} = 25 \text{ cps.}$$

The damping, *D*, of the table (Figure 2,*A* and 2,*C*) is formed by a piston, *P*, connected with the table, *T*. This piston moves in an oil-filled cylinder, *C*, which is connected with the supporting structure, *S*. There is no direct elastic connection between piston and cylinder which would influence f_1. By changing the length, *l*, by which the piston enters the cylinder, the damping can be adjusted so that $Q_{f1} = 0.7$. Due to the damping of the external tissues, R_B, ($Q_B = 2\pi f_B M_B/R_B = 2.5$), $Q_{f2} = 2\pi f_2 M_T/R_B = Q_B f_2 M_T/f_B M_B = 0.87$, i.e., close to the optimal value: $Q_{f2} = 0.7$.

At the head end of the table the calibration pendulum, *A*, is shown. It is oscillated by a motordriven eccentric. The amplitude of its mass is 0.75 cm. and the frequency is 2.2 cps. Having a mass of 1,650 grams, it produces a sinusoidal force having an amplitude of 244 grams or a peak-to-peak value of 488 grams.

An accelerometer (Calydyne model 18 B-5, not shown in Fig. 2) is connected to the table and produces a voltage proportional to its acceleration. (This instrument, like most accelerometers, measures the motion relative to a mass, not relative to the earth. The record obtained is therefore not disturbed by vibrations entering the system through the suspension, e.g., vibrations of the building, because the ballistocardiograph acts for these vibrations as a rejection filter for frequencies > 0.6 cps.). This voltage is amplified and passes through an adjustable electronic low pass filter (Krohn-Hite model 330A) and is recorded by an ink recorder (Brush BL-202). The cutoff frequency of the filter is adjusted to 15 cps. for the ballistocardiographic recording and 5 cps. for the calibration. The second pen of the recorder is used to record the electrocardiogram.

The over-all frequency response of the system could not be measured directly because no way could be found to apply upon the body known forces of the entire frequency range equivalent to the forces produced by the heart action. When a force is applied upon the body surface the force acting upon the total body mass depends on the mechanical constants of the body and those of the table. The problem was investigated by measurements on the equivalent electrical circuit. With the mechanical constants of the table M_T, E_T (loaded with the subject), R_T, and $f_B = 9$ cps., and $Q_B = 2.5$. It was found that the frequency response of the system (acceleration/force = acc/F_B as a function of frequency) is flat between 1 cps. and 15 cps. for a subject of 8×10^4 gram weight. With the assumption that f_B and Q_B are independent of the body weight (as indicated by measurements) the value of acc/f_B relative to its value at 4 cps. changes from 0.7 to 1.3 at 1 cps. and from 1.06 to 0.96 at 15 cps. with body weights from 60 kg. to 240 kg. The relatively large change at f_1 is not very disturbing because the lowest frequencies are relatively weak in the ballistocardiographic spectrum. If necessary,

however, the damping of the table could be adjusted according to the weight of the subject. By means of measurements on the equivalent electrical circuit it was also confirmed that the ballistocardiogram is not distorted by phase distortions of the system.

RESULTS

Figure 3 shows a typical record of the force F_B acting upon the body mass' i.e., the component of this force parallel to the longitudinal body-axis. The record has a simpler and clearer shape than the usual ballistocardiograms and shows two waves (I and II). Wave I occurs during systole and the beginning of diastole (compare with electrocardiogram). When we consider a probable phase shift of I caused by the internal network we may suspect that wave I is caused by the systolic heart action. For the explanation of wave II it is not necessary to assume a new impulse of force during diastole. Wave II might equally well have

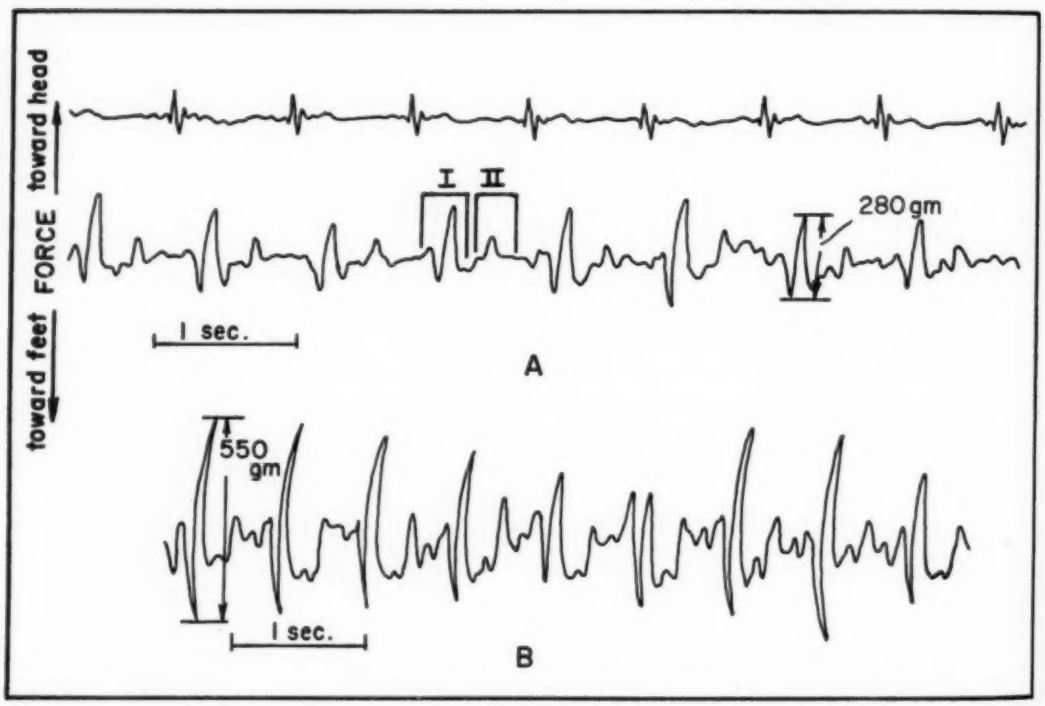

Fig. 3.—*A*. Record of F_B together with the electrocardiogram. Subject in rest. *B*. Record of F_B after the subject performed 20 kneebends.

been caused by the systolic heart action but delayed in time by the action of the internal network,[4] (actually such a network can produce any output function containing the same frequencies as the input function). To answer this question a record of the force, F_H, acting upon the heart must be obtained by the additional consideration of the action of the internal network.

To estimate the influence of the internal network on the amplitude of F_B relative to that of F_H we will compare the measured amplitude A_B of F_B ($A_B = 1/2$

peak-to-peak value of F_B = 150 grams) with the roughly estimated amplitudes A_H of F_H. They should, at the first moment that the aortic valve has opened, be in the order of:

$$A_H \sim (P_S - P_d)\, q_a = 450 \text{ grams.}$$

($P_S - P_a$ = systolic minus diastolic pressure = 6.5×10^4 dynes/cm.^{2}, q_a = cross section of the aorta $\sim$ 7 cm.^{2}). This value is probably too large because the valve does not open in infinitely short time.

On the other hand, one can estimate the amplitude of F_H as the amplitude of the inertia component (which alone is recorded by ballistocardiographic methods) of the force necessary to drive the stroke volume, S (S $\sim$ 100 cm.^{3}) out of the heart in one-fourth heart period, T (T = 1 sec.) with a velocity time course according to 1/2 sine wave of the frequency 2 cps. The velocity amplitude would be:

$$v = S/q_a \int_0^{T/4} \sin 2\pi \frac{2}{T} t \, dt = 115 \text{ cm./sec.}$$

and the amplitude of the acceleration: $acc = 2\pi \frac{2}{T} V = 1450$ cm./sec.^{2} $\sim$ 1.5 G

(G = gravitational constant = 981 cm./sec.^{2}). The acceleration of a stroke volume of about 100 grams would then produce a force amplitude of 150 grams. This value is probably too small because a part of the blood already in the aorta must also be accelerated. This amount of blood depends upon the elastic qualities of the arterial tree. Figure 3,*B* shows a F_B record of the same subject taken after 20 kneebends. The maximal force is increased by the factor 2. This increase can be produced by an increase of the stroke volume as well as by an increase of its acceleration. The periodic fluctuation of the amplitude synchronous with the heavy breathing of the subject after the exercise might be produced by a change of the heart action or by a change of the constants of the mechanical body networks connected with the breathing.

After the component of F_B parallel to the longitudinal body axis has been determined the next problem will be the recording of the resultant of F_B and its direction. These records will help to answer the question if the force which causes the ballistocardiogram originates only close to the heart or if it originates also in the peripheral circuit. Such a record can be obtained by means of a ballistocardiograph which works at least in the two dimensions of the horizontal plane.

Another problem is to determine from F_B the force F_H acting upon the heart by regarding the effect of the internal network. Until now it was possible to determine only the order of magnitude of the natural frequency, f_H, of the heart-liver complex which is elastically suspended within the body. Roentgenograms taken of a subject in lying and standing positions showed that due to gravity the heart shifts downwards about 1 cm. relative to the ribs. The natural frequency, f_o, of a spring mass system which is deflected about x cm. by gravity is:

$$f_o = \frac{1}{2\pi}\sqrt{\frac{G}{x}}.$$

For the natural frequency of the heart elastically suspended within the body is therefore found: $f_H \sim 5$ cps. Because this frequency is within the frequency range of the ballistocardiogram one might expect a remarkable influence of the internal network on the shape of the F_B record.

SUMMARY

The influence of the body mechanical system on the ballistocardiogram is discussed and a ballistocardiograph is described which is designed to give a record of the force acting upon the "total body mass." Typical and calibrated records are shown and discussed.

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FLOW THROUGH COLLAPSIBLE TUBES

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THE characteristics of flow through *rigid* tubes have been analyzed extensively by physicists and hydraulic engineers and a voluminous literature is available on this subject. The laws governing flow through rigid tubes hold satisfactorily for collapsible vessels whose lumina are sufficiently wide to permit flow at low velocities.

When fluid passes through a narrowed lumen in a *collapsible* tube, the characteristics of flow are altered abruptly. Marked effects on the nature of the stream may be noted, with the production of vibrations and with significant losses of energy. The possibility that these relationships may play a significant role in the determination of flow through stenotic orifices in blood vessels and other tubes of the body provides an impetus to define some of the parameters of this type of flow.[1]

METHODS

The essential feature of the experiments to be described consists of a study of flow through segments of soft Penrose rubber (surgical drainage) tubing. A short segment of this tubing was attached to the lower end of a column of water maintained at predetermined heights. The segment was enclosed as previously described[1] in a glass cylinder (cuff) to permit adjustments of pressure acting on the outer wall of the tube (Fig. 1). Flow was measured by a calibrated volumeter. In some experiments it was photographed as it issued from a rigid segment of brass tubing at the distal end of the elastic segment. Special instruments used for analysis of certain of the hydraulic and acoustic phenomena are described below.

RESULTS

Flow Through Elastic Tubes Without Constriction.—The effect of various heads of pressure on the flow through a segment of soft rubber tubing exposed to atmospheric pressure was recorded. In accordance with established laws of flow through rigid tubes the flow volume was related to the square root of the effective pressure head. It was thus demonstrated that within the limits of our

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experiments, flow through widely patent elastic tubes followed the laws for flow through rigid pipes. Observation of the effluent issuing from the distal end of the unit revealed a continuous unbroken quiet stream. Acoustic measurements at the site of the elastic tube elicited no vibration or sound components with amplitudes sufficient to record with a phonocardiograph.*

Partial Stenosis.—The elastic segment was partially constricted by increasing the air pressure inside the glass cylinder surrounding it (Fig. 1). Slight elevations of cuff pressure had little or no effect on the fluid delivery (Fig. 2).

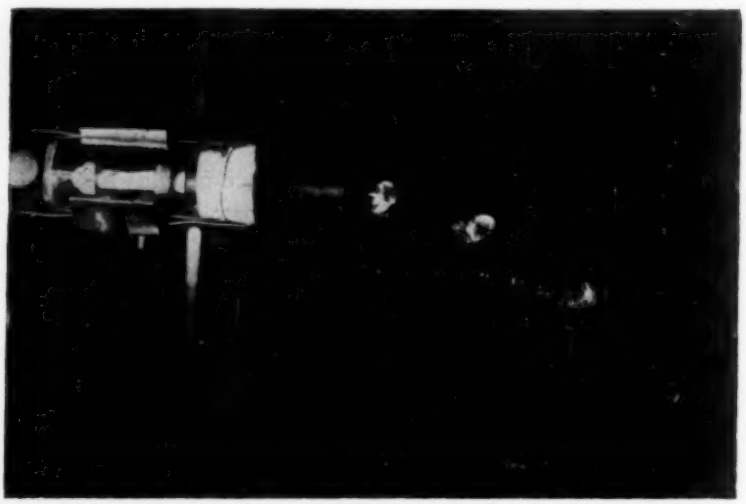

Fig. 1.—Photograph of elastic tubing with emerging drops. At the left, the glass cylinder enclosing the rubber segment is held in position by a clamp. Water passes from a reservoir (not shown) to a brass tube to which the left end of the rubber tube is fixed. The right end of the rubber tube is fixed to a second brass tube which passes through a rubber stopper out of the cylinder. Pressure in the cylinder (cuff pressure) is adjusted by pumping air through a second opening in the left stopper. The extruded drops are seen emerging and falling from the right end of the pipe. The rubber segment shows a slight indentation on its upper margin. Photograph obtained with a Strobolume through cooperation of A. J. Klapperich and W. R. Anderson of the Department of Physics, University of Illinois Undergraduate Division, Chicago.

As the degree of constriction was augmented by raising the cuff pressure, a critical point was reached at which a marked reduction in fluid discharge became evident (Fig. 2). At this point, the stream lost its continuous character and assumed an irregular appearance. Palpation of the stream gave the impression of a repetitive beating effect. Stroboscopic illumination revealed the efflux to be composed of a continuous stream of water with alternate beads and constrictions. Little or no audible sound emanated from the elastic segment.

A very slight further increase in cuff pressure, sometimes as little as 2 mm. of water, was sufficient to result in the appearance of discrete drops at the distal end of the elastic segment (Fig. 1). Each drop consisted of a relatively large head followed by a tail of progressively decreasing diameter, finally ending in a point. Fluid discharge decreased by as much as 25 per cent at this critical point (Fig. 2). A loud continuous murmur could now be heard with the unaided ear.

*This apparatus was made available through the kindness of Mr. J. Mackin of the Cambridge Instrument Company.

1. Movements of the tube: Examination of the elastic tubing at this time demonstrated a characteristic behavior. Under ordinary light the tubing seemed to be constricted partially, expecially at its distal end. Examination with stroboscopic light or by high speed motion picture photography at 4,000 frames a second revealed the elastic segment to be going through a repetitive cycle of "flitter".* Closure of the tubing occurred at its distal portion. This was followed by a sudden expansion of the tube so that it was open for an instant. The tube then progressively diminished in diameter and in this way shaped the extruded fluid into discrete drops. The wall of the elastic segment could be seen to open and close in this sequence from twenty to more than one hundred times per second.

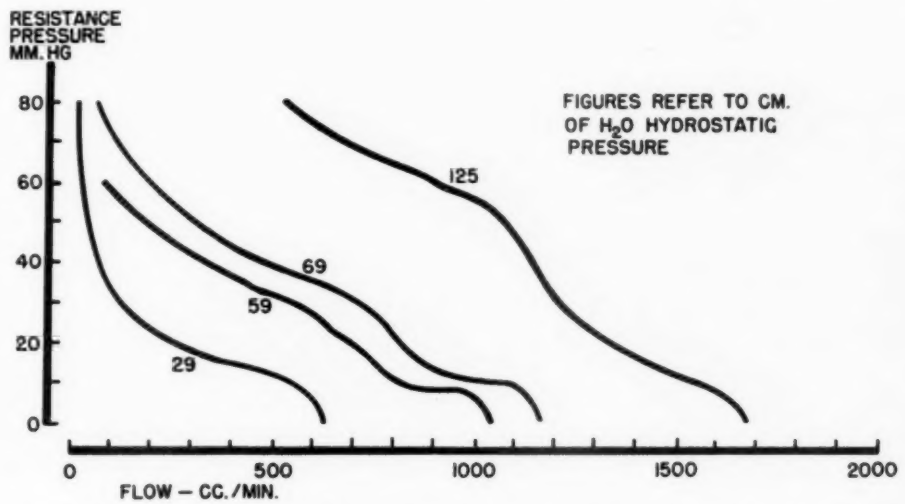

Fig. 2.—Relationship between cuff pressure (labeled Resistance Pressure) and flow for four levels of pressure head (29, 59, 69 and 125 cm. H_2O). As the resistance (cuff) pressure rises, the flow is reduced. At the point of onset of flitter, about 10 mm. Hg in the present series, a sharp reduction in flow is observed. Discussed in text.

2. Extruded drops: Photographic or stroboscopic visualization of the drops produced during flitter revealed the general shape at the moment of extrusion to be essentially the same for all conditions of driving head or cuff pressure. As each drop emerged from the apparatus it consisted of a large flattened head followed by a tail of progressively reduced diameter until it ended in a point. As cuff pressure was raised, the drops were shortened; the diameter of the head was relatively unaffected.

The differential velocities inherent in the different portions of the drop became apparent by permitting the drops to fall over a long trajectory. The drop could then be seen to take on a horseshoe shape. This U shape was due to the slower velocities resident in the head. The parabolic trajectory of the first part of the drop was less than that of later portions. As a consequence the

*In previous reports we have referred to this phenomenon as *flutter*. Since the term, *flutter*, is commonly used to describe atrial arrhythmias, we have adopted the word *flitter* to describe this phenomenon.

posterior portions, traveling at higher velocities, passed over and beyond the slower first portion producing the characteristic U formation.

High speed cinematography confirmed the fact that differential velocities inherent in the drop cause it to become deformed. The mid-portion of the drop is seen to advance into the head and distort it into a mushroom form. Spheroids could be observed at regular intervals in the drop. These tended to rise toward the upper surface, suggesting that they were gas bubbles.

3. Vibrations: Coincident with the flittering of the walls of the elastic tubing, and the production of drops a thrill was palpated and a sound heard at or near the vibrating tube.

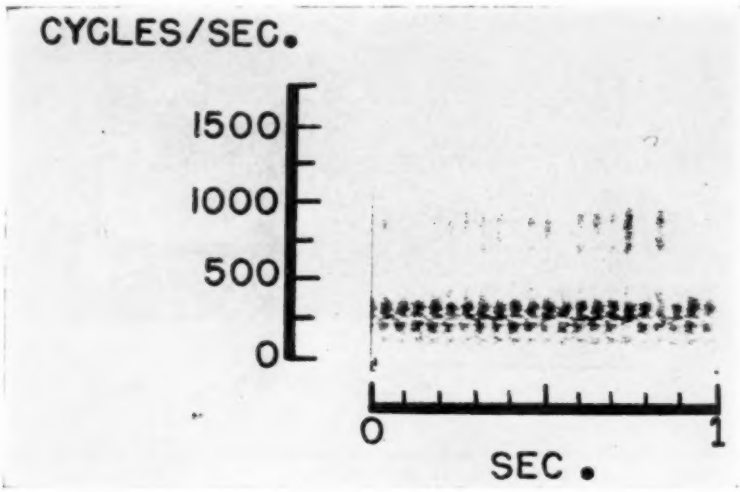

Fig. 3.—Vibration (frequency) analysis of sound produced with flitter apparatus. Repetitive bursts of sound at a rate of 21 per second are displayed. The frequencies resident in each burst show maxima at about 250 cycles per second with overtones of varying intensities at about 750 cycles per second. (Courtesy of R. R. Riesz, Bell Telephone Laboratories).

These sounds were also recorded on magnetic tape and studied by direct acoustical means and by vibration analysis. When the tapes were replayed at one-fourth the original recording speed, the murmurs originally heard as a consistent low frequency musical note of poor quality, were transformed into a series of successive transient bursts of noise similar in some respects to the noise produced by drawing a stick across a picket fence. Vibration analysis[2] revealed the sounds to be composed of intermittent bursts of energy occurring at a repetition rate equal to the flitter rate (Fig. 3). Overtones were also displayed.

4. Pressure changes: To obtain a measure of the physical forces at work in the production of flitter, the pressure in the upstream tube leading to the elastic segment was recorded directly using a Sanborn Electromanometer with a Twin-beam recorder.* The sounds produced at the instrument were recorded simultaneously. Figure 4 demonstrates the fact that each burst of sound and a silent period correspond to a single major pressure deflection. The exact correlation in time between sound and pressure changes in the system have not yet

*Courtesy of Mr. D. M. Beveridge of Sanborn Instrument Company.

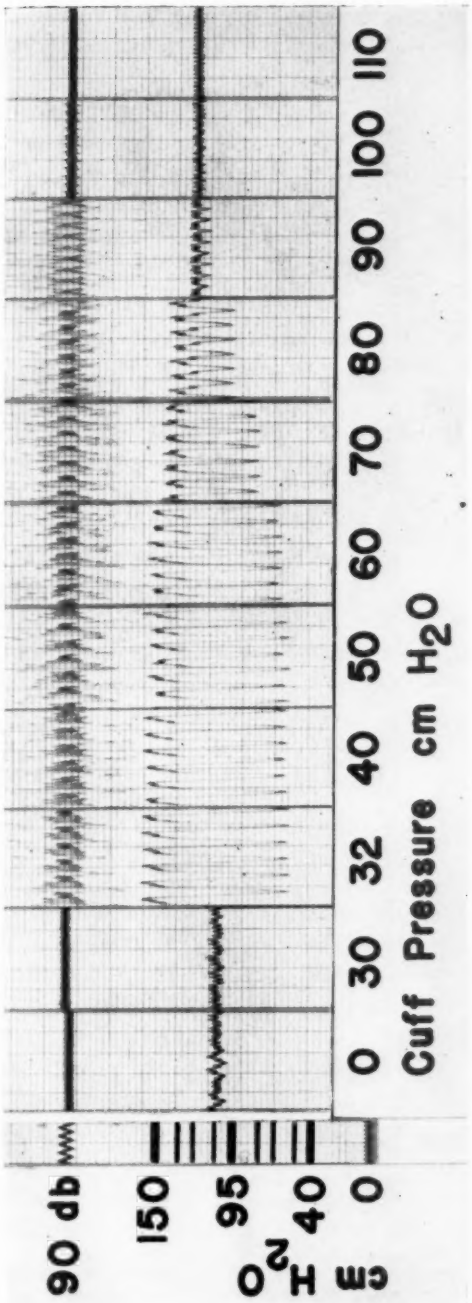

Fig. 4.—Simultaneous recording of sounds (above) and pressure changes (below) at various levels of cuff pressure, (Sanborn Twin-beam and Electromanometer). Characteristic strips (0.2 second in duration) taken from a single experiment are shown. Each vertical line presents 0.04 second. Upper tracing is calibrated by built-in 90 decibel sine wave generator. Lower curve calibrated in centimeters of water. At cuff pressure levels zero and 30 cm. water, no disturbances in flow or sound were produced. At 32 cm. water cuff pressure, the critical level, sound and pressure fluctuations are noted. The pressure changes fluctuate above and below the static pressure level, producing a type of water-hammer effect. Note that sound is composed of bursts of noise followed by brief periods of silence. At 110 cm. H_2O cuff pressure, sound and pressure changes cease. Discussed in text.

been clearly defined because of instrumental artifacts. It is likely that in our system the pressure recording lags behind the sound by about 20 milliseconds. This may be related to the length of tubing from the sound generator to the pressure transducer. Further studies will be undertaken to clarify these time relationships.

As the cuff pressure is raised by increments up to the threshold value for flitter, (32 mm. of water in the case illustrated) neither pressure changes nor sound is produced. As the threshold value is reached, flitter appears with a low repetition rate. Progressive raising of the cuff pressure results in an increased rate of repetition of the flitter process. When the cuff pressure rises above the lateral pressure at the inflow tube, flitter ceases, and the concomitant pressure fluctuations disappear (above 100 cm. water pressure in the present instance).

5. Air stream comparisons: To obtain a simpler example of the physical forces producing flitter, the effect of an air stream passing through a short segment of soft rubber tubing was studied. Under these circumstances one end of the tubing was left free, and the effect of the high velocity stream of air could be observed directly. With stroboscopic light the tube was seen to go through cycles of opening and closing apparently similar to those observed during the experiment with flow of water. When the tube was blown open it assumed a circular form. Under the influence of the stream of air the end of the tube became elliptical. The proximal walls parallel to the long axis of the ellipse approached each other and the tube closed. At this instant the walls were blown open again and an ellipse appeared with its long axis perpendicular to the preceding ellipse. The tendency for the free end of the soft tube to be pulled down by gravity introduced irregularities which sometimes made it difficult to follow the movements.

A clearer representation of the cycle of events was obtained by utilizing a segment of somewhat heavier rubber tubing, flattened at either lateral margin, of the type utilized in "duck-bill" valves. Stroboscopy demonstrated that the flow of air through the tube caused the ends of the segment to be alternately opened and closed as with the softer tubing (Fig. 5).

Concurrent with the flittering of the end of the tube at frequencies ranging from 40 to 300 per second, a "woodwind sound" of poor quality was heard. Increased intensities were obtained by an increase in air pressure. Repetition frequency was raised by reducing the diameter of the outlet.

The events taking place in the collapsible segment perfused with water appeared more complex. This was due in part to the fact that both ends of the Penrose segment were fixed securely to cylindrical brass tubes. Collapse of the rubber tube usually occurred at its distal end. Since this end was maintained circular by the rigid brass tube, the Penrose segment puckered as it contracted and closed. The momentum of the stream carried the closed segment slightly into the rigid outlet tube. As the tube was blown open, a wave passed across the

Fig. 5.—Motion pictures of movement of an elastic tube, recorded at 4,000 frames per second (Fastax Camera). Each fourth frame is shown. Air was blown under constant pressure from a source at the left. The longitudinal aspect of the tubing is shown under *A*. By means of a mirror, the end of the tubing is seen simultaneously at *B*. The lips of the tube were marked with point dots to facilitate analysis. A constriction appears in the tube and progresses until it is completely occluded. Air then moves under pressure to blow the tube open as in frame *21*. The cycle is then repeated. Obtained with the cooperation of Dr. Paul Moore, School of Speech, Northwestern University.

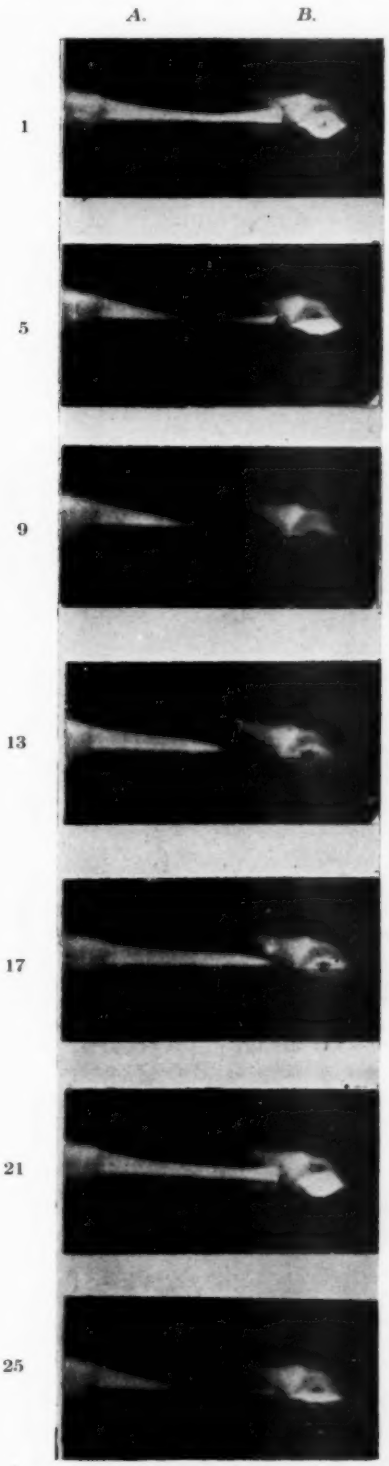

Fig. 5. *(For legend see opposite page.)*

Penrose segment from the outlet to the inlet tube. This wave was reflected back and forth along the elastic segment until the tube closed during the succeeding cycle at which time a new propagated wave front was initiated. These "overtones" could be followed by means of high speed cinematography. Details of a drop extruded from the apparatus under these conditions are illustrated in Fig. 6.

6. Parameters: Some of the parameters of the flitter mechanism were investigated. The volume discharge through the Penrose segment was roughly related to the pressure head. However as the cuff pressure was raised, the curve could be shown to have at least several segments of differing slope (Fig. 2). When the cuff pressure was higher than the lateral pressure measured at the inflow tube to the elastic segment, a seepage flow was continuous, though minimal, and no flitter could be observed. As the cuff pressure was permitted to fall to

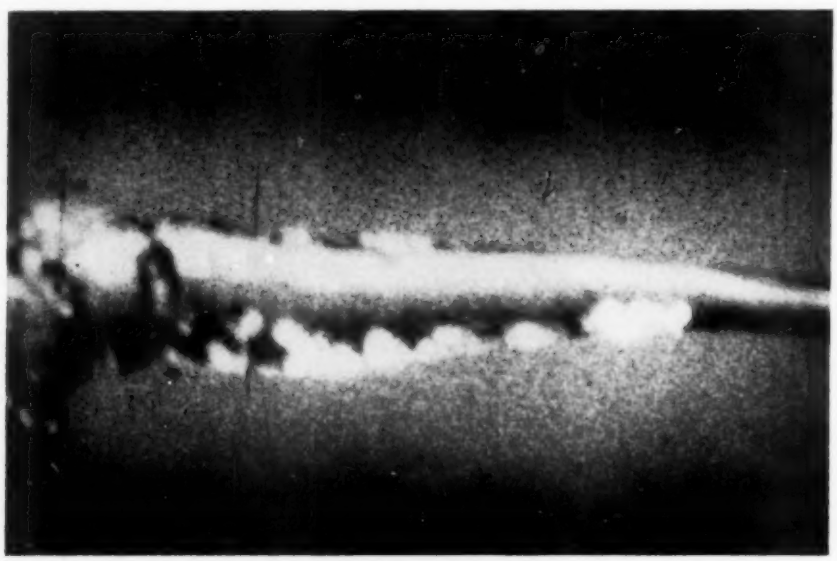

Fig. 6.—Closeup of drop produced by flitter apparatus. (Cinematography at 4,000 frames per second). The drop is seen to have a large head at left, deformed in part by gravitational pull and by movement of posterior portions of drop into its head. Round shadows which may represent bubbles of gas produced by cavitation are seen in the neck. The tail of the drop tapers off to a point (not shown).

the level of the lateral (systolic) pressure at the site of the elastic segment, flitter at high frequencies began, and flow increased perceptibly. Further reductions in cuff pressure resulted in changes in the flitter frequency and in the intensity of the sound produced. As the cuff pressure fell to still lower levels a critical point was reached at which flitter ceased and flow increased markedly. At cuff pressures below this point no further effect on flow was noted; the stream was continuous and relatively quiet.

The primary factors in the production of flitter in collapsible tubes can be shown to depend on the relationship between lateral pressure and the degree of compression of the tube by ambient or cuff pressure. A number of other

factors were studied but these had a lesser influence on the characteristics of the mechanism. These included the length, thickness, and diameter of the Penrose rubber tubing, and the specific gravity, temperature, viscosity, and surface tension of the fluid. The stiffness of the tube affected the amount of extrinsic pressure required before flitter was initiated. The addition of resistances beyond the the elastic segment produced special effects which will be described separately.

DISCUSSION

The present study provides a basis for an analysis of the characteristics of flow through collapsible vessels. When such vessels have no region in which high velocity flow takes place, conditions of flow are similar to those obtained in flow through rigid pipes. The presence of a partial constriction in the tube introduces new characteristics which markedly affect the conditions of flow. At a critical degree of constriction, produced by an increase in the level of cuff pressure, the pattern changes from quiet flow, seen as a smooth continuous stream, to an apparently irregular stream producing considerable vibration and noise. With stroboscopic illumination or high speed cinematography the smooth stream can be seen to be converted from an intact continuous column into a series of discrete drops. The formation of these drops is secondary to movements of the vessel wall. The increased velocity through the stenosed segment is coincident with a reduction in the lateral pressure at the site of narrowing as in a Venturi tube.

Bernoulli's principle holds that for a given mass of fluid, the sum of the energy expressed as lateral pressure plus that expressed in flow (velocity) must equal the static driving head (neglecting friction); when either lateral pressure or velocity increases, the other must decline by an equivalent amount. In our present studies, the production of an area of narrowing of a rubber segment sets the stage for an increased velocity and a consequent fall in lateral pressure in the narrowed region. With the fall in lateral pressure, the walls of the rubber segment tend to collapse and this creates the conditions for a higher velocity, a further drop in lateral pressure, and progressive closure. When the tube is almost completely collapsed by this process, flow ceases and the total head becomes available as lateral pressure. This force blows the tube open, flow begins again, and the flitter cycle is repeated. The characteristics of flitter produced by flow of liquids differ from those produced by flow of gases primarily by the greater specific gravity and incompressibility of liquids.

Study of the flitter mechanism may have importance in the understanding of purely physical problems, as well as in the study of flow problems in physiology and medicine. The characteristics of flitter are apparently related to the mechanism of reed musical instruments, in particular the double reeds, the shawm, bassoon, and oboe. The tremendous resistance of flow through such reeds may be related in considerable part to the marked energy loss due to the initiation and maintenance of the flitter mechanism. Closely related to these problems are the characteristics of the motion of the vocal cords which are "set" by the tension of the laryngeal muscles,[3,4] but are made to vibrate by being blown open and shut

by the bronchial air blast.* The passage of gases at high velocities through narrowed regions in the tracheobronchial tree and the gastrointestinal tract also give rise to flitter effects, such as snoring, rhonchi, borborygmi, and the like.

The energy losses attendant upon the flitter mechanism play significant roles in the delivery of blood to various organs. For example, the vibrations noted in coarctation of the aorta apparently have their origin in a similar mechanism operating at the stenotic site. The discrete jetlike flow through the flittering orifice, apparently accounts for the anacrotic incisura often seen in this condition.[5] The murmur of arteriovenous anastomoses may also arise from the high velocity of blood passing through the abnormal connection between the artery and the vein. The Korotkoff murmurs heard when arteries are compressed during measurement of the blood pressure are probably also due to flitter of the walls.[6] The intensity of the sounds and their harmonic patterns also depend on the relationships between lateral pressure, velocity, and the diameter and nature of the lumen through which the fluid is passing. Present unpublished studies in our laboratory give evidence of remarkable similarities between the acoustic patterns of flitter and such murmurs as are heard in patent ductus arteriosus and aortic stenosis.

It may be of considerable importance that the forces at work in the production of these murmurs may also contribute to the process of progressive stenosis. No adequate concept has been advanced to explain why stenosis appears to be an inexorably progressive process, despite torrential flows of blood at high pressures and velocities through such narrowed orifices. Yet, surgeons have found that simple pressure with the finger is often adequate to cause stenotic valve leaflets to fall away from each other and return the valve to a relatively normal state.

In the present concept, the stenotic tendency is seen to be facilitated by the increased velocity at the site of narrowing; the lateral pressure factor which ordinarily assists in maintaining the diameter of blood vessels and orifices is thereby reduced. In this way, the wall of the vessel or the valve margins is released from the normal lateral pressure and progressive closure ensues. Experimental verification of this concept in studies on dogs has already been obtained.[7] This effect, plus the injury which may be produced by the striking of the opposite walls against each other during flitter, may stimulate proliferation of the connective tissues and contribute to the progression of the stenosis.

In the face of the possible significance of the special physical characteristics of flow through such collapsible vessels as arteries, veins, and valves, it is remarkable that little actual data on this type of flow are available. Numerous workers in physiology have utilized the unit described in the present communication, but for the most part they have had little interest in the nature of the repetitive phenomenon which we have analyzed.[8-13] Usually, these workers have taken special precautions to eliminate the "bumping" or "flutter" of the apparatus.[14-18]

Physicists and engineers have studied a large variety of special cases involving relaxation oscillations similar in some respects to those analyzed in the

*Some qualitative data on flow through an artificial larynx have been published. These show that opening and closing of an artificial larynx produce discrete "puffs". R. T. Garhart: Airflow Through the Larynx, Quart. J. Speech **26**:606, 1940.

present study.[17-21] However, little information is available in the fields of hydrodynamics, sound and vibrations which is pertinent to the special case posed by the problem of flow through collapsible vessels.

The importance of the special properties of pressure-velocity relationships operating in collapsible tubes is suggested by our studies. Further analyses of the hydrodynamic and acoustic phenomena involved in the repetitive behavior produced by flow through collapsible vessels would appear to be indicated.

SUMMARY

Flow through a partially stenotic collapsible vessel sets up a repetitive phenomenon of opening and closing of the tube. Drops of a specific shape are extruded as a result of this intermittent motion of the tube, and sounds with a murmurlike quality are produced. Energy losses, easily measured as changes in the volume flow produced by a given pressure head, may be marked. These physical phenomena were studied by means of models, utilizing pressure and sound recordings, stroboscopy and high speed cinematography.

The mechanism of murmur production is seen as due to the repetitive interchange, at rapid rates, of the energy of the stream from *lateral pressure* to *velocity*. This is brought about by the changes in the diameter of the tube. The importance of these phenomena in the elucidation of the mechanisms of murmur production and in the progression of stenotic lesions is discussed.

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FUNCTIONAL CARDIOVASCULAR DISTURBANCES—THEIR RESPONSE TO DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

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REINDELL[1] and Delius[2] have classified neurocirculatory asthenia, the most commonly occurring form of functional cardiovascular disturbances, into two types: (a) hypertonic, and (b) hypotonic. However, we found employing the physical method of Frank[3,4] that disturbances of the entire cardiovascular system occur in addition to blood pressure changes. A comprehensive review of the clinical picture of neurocirculatory asthenia may be found in the following papers of Wezler and Boeger,[5-7] Delius,[2] Reindell and Bayer,[8] Schimert,[9-12] Zickgraf,[13] Cerulli,[14] Wolf,[15] Weiss,[16] and Walker.[17]

Fundamentally, two extremes in the behavior of the cardiovascular system may be found with transitory stages being present between the normal state and the following pathologic extremes:

Ergotropic State.*—This group of patients is characterized by a hyperresponsive cardiovascular system with a moderately elevated blood pressure, a typically increased pulse pressure amplitude, high stroke and minute volume, and tachycardia in the presence of lowered peripheral resistance. The calculated work output of the heart is increased above normal. These are the cardiovascular changes that occur in the "ergotropic" states as described by Hess.[18]

Histotropic State.*—This group of patients is characterized by a markedly reduced circulatory state with hypotension, a low pulse pressure amplitude, decreased stroke and minute volume in the presence of elevated peripheral resistance. Generally, this state is typified by physical and emotional relaxation, the extreme of which is sleep, and was named by Hess[18] as the "histotropic or trophotropic-endophylactic state."

The basis of neurocirculatory asthenia is the deficiency of purposeful correlation between the demands of the environment and the response of the cardiovascular system. A simple classification into "sympathicotonic" or "vagotonic" response according to Eppinger and Hess[19] is unsatisfactory because patients in either group exhibit disturbances of both divisions of the autonomic nervous system. Von Bergmann[20] described the mixed type of response as "amphotonia" or vegetative stigmatization. The mechanism of amphotonia is probably the result of the following factors:

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*The terms "ergotropic" and "histotropic" are used in the sense of W. R. Hess[18] to indicate states of increased expenditure of energy (ergotropic) in contrast to state of conservation and/or recovery of energy (histotropic).

1. The central, predominantly hypothalamic control of the autonomic nervous system does not activate either the sympathetic or parasympathetic separately but precipitates a specific targeted reaction complex involving both sympathetic and parasympathetic elements in synergy.[18]

2. Abnormal changes in the reaction level of one part of the autonomic nervous system (sympathetic) always give rise to compensatory reactions of the other part (parasympathetic).[20-23]

3. Excitation of the autonomic nerve endings in the periphery resulting from a focus of infection or other stresser factors may at any time disturb the controlling regulatory centers.

It would appear, therefore, that it is almost impossible to treat even an apparently one-sided vegetative disturbance with an individual sympathicomimetic, sympathicolytic, parasympathicomimetic or parasympathicolytic drug. This consideration influenced Rothlin[21] in 1934 to develop a combination of drugs exhibiting sympathicolytic (ergotamine*) and parasympathicolytic (Bellafoline†) properties combined with a brain stem sedative (phenobarbital). Pharmacologic studies have shown that the actions of the two neuro-inhibitory drugs exercise their effects uninhibitedly on their respective systems and potentiate the central sedative action of phenobarbital.

Clinical investigations by Bickel,[24] Jores and Goyert,[25] Mayerhofer,[26,27] Smilowitz,[28] Mauderli and Magg,[29] Di Benedetto,[37] Harris,[38] MacFadyen,[39] Yontef,[40] Kavinoky,[41] Wittich,[42] Favata[43] and others have shown that this combination benefits patients whose symptoms reflect sympathicomimetic or parasympathicomimetic predomination as well as it does those suffering from a classical amphotonic condition. Our clinical experience through many years has led us to try to determine how Bellergal influences the regulatory dysfunction in neurocirculatory asthenia.

Steinmann and associates,[30] utilizing the methods of Boeger and Wezler,[6] found that ergotamine tartrate administered orally or subcutaneously to normal individuals always produced a fall in stroke and minute volume, an increase in peripheral resistance with inconsistent changes in blood pressure. A combination of ergotamine and Bellafoline with or without phenobarbital produced almost the same effects. Therefore, it was assumed that the primary action of this combination is that of ergotamine.

It is our belief, and that of others, that autonomic circulatory disturbances may be of two types and that each of these types responds to stress in a different way. Since a study on normal persons did not entirely satisfy us, we decided to extend the investigations of these drugs individually and in combination to both the extreme "histotropic" and "ergotropic" groups of individuals, in short- and long-term experiments.

MATERIAL AND METHOD

The hemodynamic response to Bellergal and its individual components in forty individuals with neurocirculatory asthenia was studied. The following criteria were studied according to the formula of Broemser and Ranke:[31] (1) pulse wave velocity; (2) duration of diastole and systole; (3) systolic and diastolic blood pressures computed according to Korotkoff. Aortic diameters were taken

*Ergotamine = ergotamine tartrate. Trade name Gynergen.

†Total levorotatory alkaloids of belladonna (as malates) calculated as l-hyoscyamine.

from Suter's tables,[32] pulse waves were recorded by an air-conducting sphygmograph on a photokymograph. Also determined were minute volume, stroke volume, peripheral resistance and elastic resistance (see under results).

We chose the procedure suggested by Frank[3,4] for the physical analysis of the circulatory system since we believe that it is the only method presently known which supplies truly objective data without undue manipulation of the patient and alteration of the basic state. Tests can be done rapidly and repeatedly and a maximum number of circulatory criteria are obtained. Recent comparisons of the physical methods of stroke volume determination used by us and the direct measurements according to the Fick principle have shown good agreement.[35,36] A comparison of the stroke volume values by Deppe and Wetterer[33,34] calculated according to the formula of Broemser and Ranke[31] with the values obtained with induction tachography revealed a discrepancy of only ± 15 per cent. Since our investigations were primarily concerned with the relative shift in the initial responses of the patients, we believe our data allow certain conclusions.

Patients in a basal state reclined on an examining table until the blood pressure and pulse rate were constant. The blood pressure cuff was applied at the start of the rest period and left in place in an effort to eliminate psychogenic effects caused by repeated application and removal of the cuff; in addition, patients were not aware at which particular instant blood pressure was taken. In the labile individual these tests were performed many times on the same day as well as on different days before starting therapy. It is important to achieve consistency of the circulatory values so that changes developing during therapy will have significance.

Twenty-one individuals were treated with Bellergal or its components for a short-term test. Twenty-three others received four to six tablets Bellergal daily for a long-term experiment. Some individuals were changed from Bellergal to its individual components so that the total number of tests is higher than the number of individuals treated.

RESULTS

Explanation of the symbols in the text and graphs:

P_s and P_d = systolic and diastolic pressure; normal average = 140 mm. Hg/80 mm. Hg
V_S = stroke volume in cubic centimeters; normal average 67 c.c.
F_r = frequency per minute; normal average 72 beats per minute.
V_M = minute volume in 1000 c.c. or liters; normal average = 4.6 liters.
C_A = pulse wave velocity in the aorta, in meters per second. Normal average = 5 to 8 M./sec.
E = elastic resistance in dynes/cm.^{5}; normal average = 900 dynes/cm.^{5}
W = peripheral resistance in dynes sec./cm.^{5}; normal average = $1{,}800 \frac{\text{dynes sec.}}{\text{cm.}^5}$.

The relatively small number of short-term tests in the twenty-one patient group consisting of six to seven experiments each with Gynergen, Bellafoline, phenobarbital and combinations thereof do not permit statistical evaluation. However, this series did reveal that the pharmacodynamic properties of the individual drugs vary markedly in different types of cardiovascular disturbances. Tables I and II show the changes in the circulatory factors as a result of administering these drugs in a short-term experiment. The varying and partly reverse action in the two types of neurocirculatory asthenia are evident.

Observations With The Individual Drugs.—

Ergotamine tartrate intravenously: The characteristic action of this agent is shown in Table I. Therapeutic doses of 0.1 to 0.5 mg. intravenously lower the stroke and minute volume and increase the peripheral resistance in the "ergotropic", the normal, and the majority of the "histotropic" subjects. The average blood pressure remains unchanged. In the "ergotropic" and the normal individuals, the pulse wave amplitude is slightly decreased. The decrease of the cardiac minute volume results in part from the fall in the stroke volume and in part from the decrease in pulse rate.

TABLE I.

	STATE	GYNERGEN 0.1–0.2 mg. I.V.	BELLAFOLINE 0.1–0.2 mg. I.V.	SOD. PHENOBARB. 0.01–0.02 GM I.V.	GYNERGEN 0.1 MG. BELLAFOLINE 0.1 MG. āā I.V.
Pm = mean blood pressure	ergotropic normotonic	+ −	+ −	(−) if elevated	(+) −
	histotropic	(+) extreme cases	+ −	+ −	+ −
P Δ B.P. amplitude	ergotropic	−	−	− −	−
	histotropic	− (+) extreme cases	+ −	+	(+) −
Fr. = heart rate	ergotropic	−	−	− −	−
	histotropic	(+)	+ −	(+)	+ −
V_S = stroke volume	ergotropic	− −	−	− −	−
	histotropic	(∓) extreme cases	+ also normotonic	+	+ − (− in extr. cases)
V_M = minute volume	ergotropic	− −	−	− −	−
	histotropic	+ extreme cases	+ also normotonic	+	+
W = peripheral resistance	ergotropic	+	+	+	+ +
	histotropic	−	−	−	− − particularly in extreme cases

āā = of each
I.v. = intravenously

Figure 1 shows the action of 0.1 mg. ergotamine tartrate intravenously in a moderately "ergotropic" patient. The stroke volume decreases from 80 c.c. to about 40 or 50 c.c. accompanied by a fall in the pulse wave amplitude. Then minute volume dropped from 6 to 4 liters; the peripheral resistance increased two fold. Work output of the heart calculated from the average arterial pressure

TABLE II.

NO.	NAME	AGE	Pm		Ps-Pd		Fr		Vs		Vm		W		DOSES mg. *	TIME OF GE	STATE
			BEFORE	GE	BEFORE	GE	BEFORE	GE	BEFORE	GE	BEFORE	GE	BEFORE	GE			
944	F. W.	36	97.5	120	75	60	80	48	115	53	9.2	2.5	850	2780	L 20.0 G 0.25 B 0.125	7′	ergotropic
1008	H. G.	24	95	95	50	30	94	73	62	39	5.2	2.8	1300	2680	"	8′	"
794	I. M.	24	117.5	107.5	45	35	92	72	59	35	5.5	2.5	1725	3415	L 40.0 G 0.5 B 0.2	2′	normal
1021	C. S.	29	97.5	95	35	40	65	52	55	49	3.6	2.5	2180	2990	L 10.0 G 0.125 B 0.06	3′	"
876	J. Z.	41	125	137.5	50	55	99	91	84	88	5.4	8.0	1860	1375	L 40.0 G 0.5 B 0.2	5′	"
856	A. G.	27	95	90	30	20	77	59	45	27	3.4	1.6	2210	4500	L 40.0 G 0.5 B 0.25	7′	histotropic
1056	I. S.	22	107.5	105	35	30	65	74	49	32	3.2	2.3	2730	3590	L 10.0 G 0.125 B 0.06	10′	"
955	E. M.	29	80	92.5	30	25	67	56	41	32	2.7	1.8	2060	4180	L 20.0 G 0.25 B 0.125	6′	"
943	H. L.	26	110	112.5	40	35	53	45	43	35	2.3	1.6	3840	5950	"	3′	"
966	R. S.	61	87.5	82.5	45	45	78	69	36	65	2.6	4.5	2480	1460	"	5′	"

Effect of one intravenous injection of Bellergal (10-40 mg. Sodium phenobarbital, 0.25-0.5 mg. Gynergen and 0.06-0.2 mg. Bellafoline) in 10 subjects with varying circulatory reaction. Each row of boxes presents the circulatory factors before the experiment and at the point of greatest effect (G.E.). The next to the last row of boxes indicates the time of greatest effect.

PM = mean arterial pressure; Ps-Pd = pulse amplitude = pulse pressure; Fr = pulse frequency; Vs = stroke volume in c.c. Vm = minute volume in 1,000 c.c.

W = peripheral resistance in $\frac{\text{dynes sec.}}{\text{cm.}^5}$

*L = sodium phenobarbital; G = Gynergen; B = Bellafoline

and the stroke volume dropped considerably in almost all cases. The decrease in cardiovascular function (minute/stroke volume) is manifested more clearly the greater the degree of "ergotropism". An exception is seen in the cases of extreme "histotropism" in which doses of 0.1 to 0.5 mg. of ergotamine tartrate will increase stroke and minute volumes.

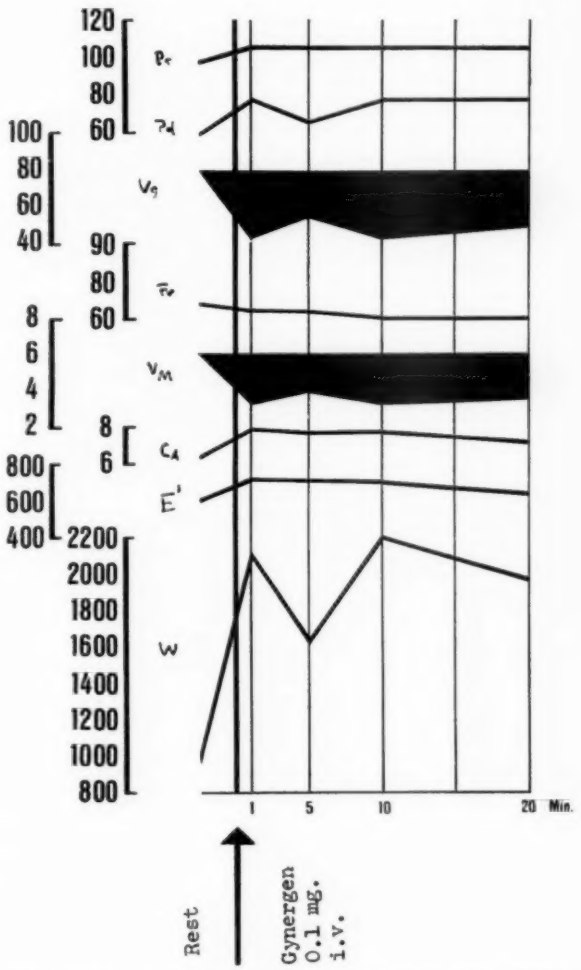

Fig. 1.—Effect of 0.1 mg. Gynergen intravenously in an "ergotropic" patient. C. G., aged 30, "Vegetative Dystonia".

The effectiveness of small doses of ergotamine tartrate orally was tested in three individuals. The "ergotropic" patients reacted to oral doses of 0.6 mg. ergotamine tartrate (equivalent to the ergotamine in two tablets of Bellergal) with a definite drop in stroke and minute volume accompanied by an increase in peripheral resistance after 25 to 30 minutes.

Bellafoline intravenously: The action of the parasympathicolytic Bellafoline (see Table II) is even more dependent upon the initial state of the circulatory

*L = sodium phenobarbital; G = Gynergen; B = Bellafoline

system than is the case with Gynergen. In the "ergotropic" state, Bellafoline reduces the stroke and minute volumes while raising peripheral resistance. This effect, however, is less marked than in the case of ergotamine tartrate. In the "histotropic" state, the stroke and minute volumes are definitely increased. The increase in stroke volume equals about 30 per cent. Figure 2 shows this behavior in the form of a curve.

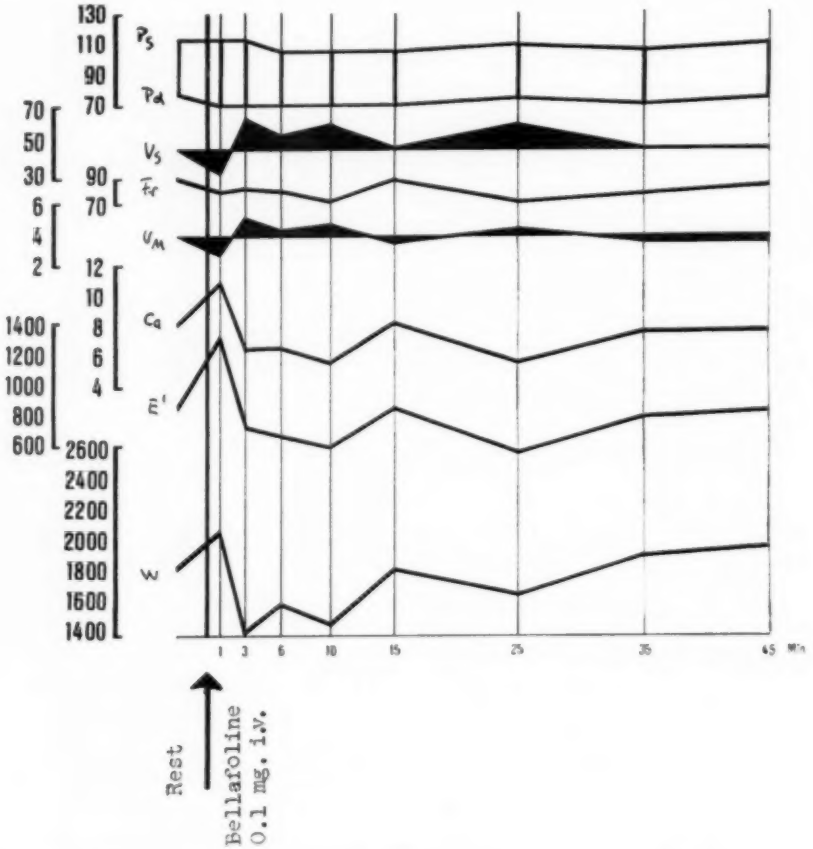

Fig. 2.—Effect of 0.1 mg. Bellafoline in a "histotropic" patient. E. T., aged 27, "Vegetative Dystonia".

Investigations in the same individual with Bellafoline and ergotamine tartrate carried out on separate days showed that in the "ergotropic" individual both drugs evoked a fall in cardiac work output. In the "histotropic" patient, however, ergotamine reduced minute volume, while Bellafoline usually raised it.

Phenobarbital intravenously: The effects of phenobarbital on circulation described previously by the author likewise are dependent upon the initial state of the cardiovascular system. Small doses insufficient to cause sleep produced a slight shift in the circulatory response towards the "histotropic" state. In the "ergotropic" state, however, small doses of 0.01 to 0.02 Gm. (intravenously): (1) reduce the elevated stroke and minute volumes; (2) reduce the pulse rate;

(3) increase peripheral resistance. The "ergotropic" type circulation is completely normalized, sometimes even changed towards the "histotropic" state (see Table I). In the presence of a frank "histotropic" state, an occasional increase in the stroke and minute volumes has been observed.

Combinations of Ergotamine Tartrate and Bellafoline Intravenously.—In the "ergotropic" state, a combination of ergotamine and Bellafoline definitely lowers stroke volume and reduces pulse rate thus decreasing the minute volume (Table I). A similar response is seen in the normal person. In the extreme "histotropic" state, an increase in stroke volume sometimes occurs together with an increase in pulse rate. Our results with the combination of ergotamine and Bellafoline confirm the work of Steinmann and associates[30] in normal individuals.

Combination of Bellafoline, Ergotamine Tartrate and Phenobarbital Intravenously.—This combination was tested in ten individuals in short-term experiments and varying states of the cardiovascular system. A fresh mixture of sodium phenobarbital, ergotamine tartrate and Bellafoline in liquid form containing the individual components in the same concentration as in Bellergal tablets was prepared. This enables a comparison between effects obtained from oral and intravenous administration. The intravenous preparation obviously produced more immediate effects but sometimes resulted in unpleasant side effects. The results of these short-term tests are recorded in Table II. There were three normal persons, two "ergotropic" and five "histotropic" patients. In the "ergotropic" type, the effect of Bellergal is clear: the minute volume decreases from 9 to 2.5 liters in the first case (944) and from 5.2 to 2.8 liters in the second case (1008) due to a decrease in stroke volumes and pulse rates. The pulse pressure is lowered in both cases and the blood pressure varies. In the normal persons, two responded with a fall and one with a slight increase in stroke and minute volumes (No. 794, 1021, 876). In the "histotropic" group (No. 856, 1056, 955, 943, 966) four responded with a further decrease of their already reduced circulation, whereas one (966) increased his minute volume from 2.6 to 4.5 liters. The blood pressures and amplitudes did not change significantly. These observations would indicate that in the acute experiment with the complete preparation Bellergal, a depression of all circulatory functions is predominant irrespective of the initial state (ergotropic, histotropic, or normal).

Figure 3 shows the action of the complete preparation. In contrast to the action of the individual components, Bellergal intensifies and prolongs the depressant action on the circulation in the "ergotropic" state. The same figure also reveals the difference between the short-term and the long-term effects of this preparation. Figure 3, *B* shows the change in circulation which follows the administration of two tablets three times a day for 6 days. The transient decrease in circulation in the acute experiment is modified to a permanent change in the basic circulatory state.

Long-Term Tests With Bellergal (Oral).—Twenty-three patients with different circulatory states but with a definite diagnosis of neurocirculatory asthenia received two tablets of Bellergal twice a day for a period lasting up to 4 weeks. Results are shown in Table III. This group included ten "ergotropic" pa-

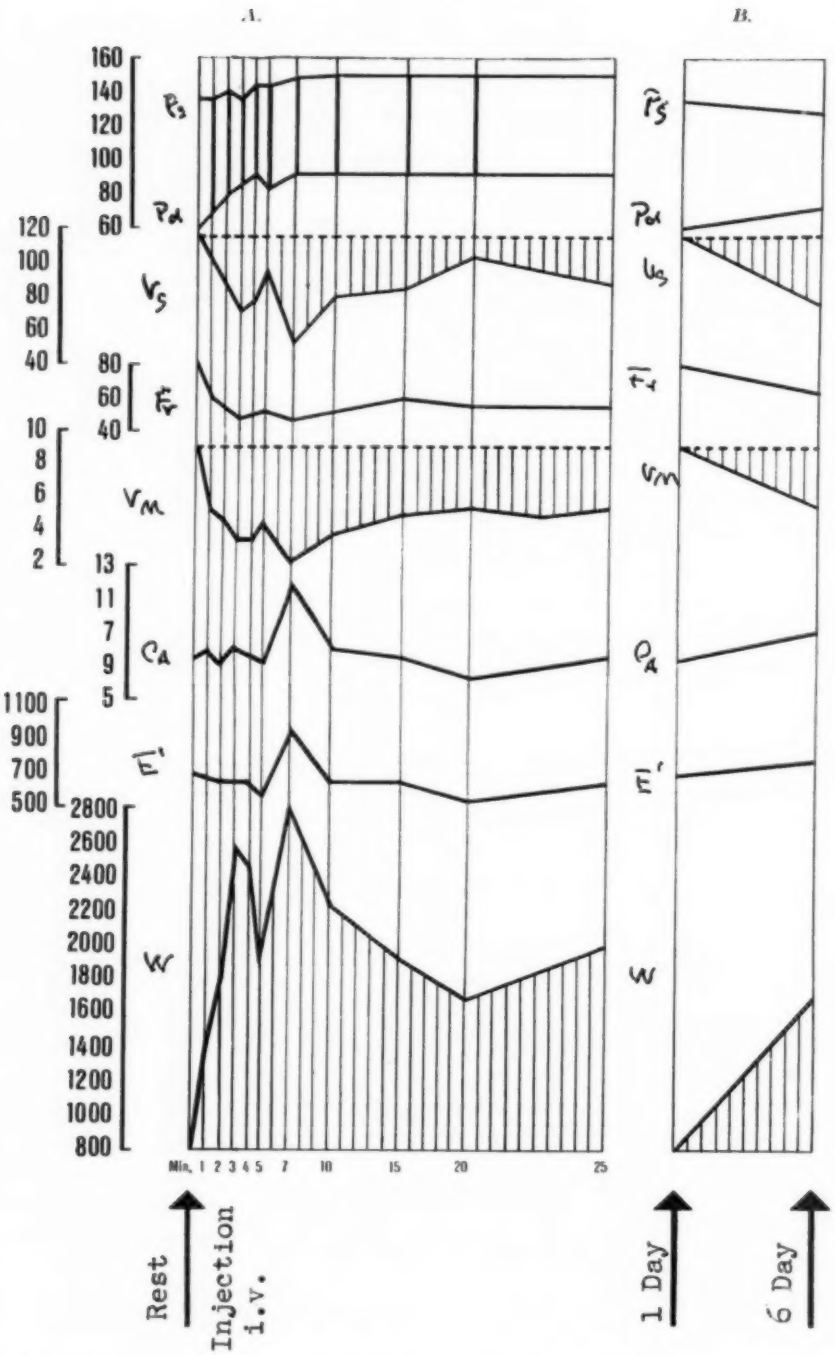

Fig. 3.—Effect of Bellergal in short- and long-term experiment ("ergotropic" status). W. F., aged 36, *A*. Intravenous injection of Sodium phenobarbital 20 mg., Gynergen 0.25 mg., and Bellafoline 0.125 mg. (corresponding to one tablet of Bellergal). *B*. Circulatory criteria before and after oral treatment with two tablets of Bellergal three times a day for 6 days.

TABLE III

NAME	AGE	B.P.	FR.	V_S	V_M	W	*	STATE
F. W.	36							
Before		135/60	80	115.0	9.0	850	↓	ergotropic
After 6 days Bellergal		130/70	65	74.0	4.7	1700	++	
H. T.	28							
Before		110/70	94	76.0	7.1	1005	↓	"
After 16 days Bellergal		105/80	57	40.4	2.3	3180	+	
H. G.	24							
Before		120/70	94	62.0	5.8	1300	↓	"
After 10 days Bellergal		105/70	75	30.3	2.3	3085	++	
F. S.	63							
Before		145/90	75	83.0	6.2	1511	↓	"
After 7 days Bellergal		115/70	60	82.1	4.9	1580	+	
T. H.	69							
Before		150/80	96	107.8	10.4	889	↓	"
After 12 days Bellergal		135/90	92	63.6	4.4	2060	++	
G. A.	24							
Before		165/85	83	113.0	9.38	1065	↓	"
After 28 days Bellergal		150/80	57	81.6	4.65	1965	++	
S. M.	24							
Before		135/80	98	142.7	13.9	606	↓	"
After 21 days Bellergal		115/85	87	63.0	5.53	1445	++	
L. S.	43							
Before		140/78	70	87.5	6.12	1425	↓	"
After 14 days Bellergal		138/76	67	65.1	4.37	1970	+	
M. K.	29							
Before		122/74	106	98.8	10.48	748	↓	"
After 28 days Bellergal		114/72	93	72.9	6.78	1095	++	
J. S..	33							
Before		130/65	78	102.8	8.02	972	↓	"
After 28 days Bellergal		125/70	65	65.4	4.25	1835	++	
Average:								
Before		135/75	87	98.8	8.64	1041		
After treatment		123/76	71	63.8	4.41	1991		
J. B.	60							
Before		155/95	75	49.7	3.7	2680	↑	normotonic
After 7 days Bellergal		150/90	66	102.0	6.7	1430	−	

TABLE III (CONTINUED)

NAME	AGE	B.P.	FR.	V_S	V_M	W		STATE
M. P.	55							normotonic
Before		140/75	69	67.5	4.7	1850	↑	
After 18 days Bellergal		140/80	70	112.0	7.8	1125	+	
B. U.	38							
Before		100/75	72	48.7	3.51	1995	↓	"
After 20 days Bellergal		100/77	78	38.4	3.0	2390	o	
C. B.	36							
Before		120/85	89	58.9	5.24	1565	↓	"
After 12 days Bellergal		135/85	87	50.9	4.43	1990	+	
E. H.	17							
Before		110/80	98	32.0	3.13	2420	↑	"
After 28 days Bellergal		120/75	91	47.4	4.27	1825	+	
A. G.	45							
Before		140/100	73	59.0	4.30	2230	↓	"
After 28 days Bellergal		130/90	65	49.5	3.22	2730	−	
Average								
Before		127/85	79	52.6	4.09	2106		
After treatment		129/83	76	66.7	4.90	1915		
H. M.	29							
Before		95/65	67	40.0	2.7	2000	↓	histotropic
After 16 days Bellergal		105/60	61	76.0	4.6	1400	o	
R. S.	61							
Before		110/65	78	36.0	2.8	2500	↑	"
After 21 days Bellergal		105/65	63	53.0	3.4	2000	++	
H. L.	26							
Before		130/90	53	43.0	2.3	3800	↑	"
After 6 days Bellergal		120/85	69	42.0	2.9	2800	o	
P. G.	27							
Before		145/105	65	41.5	2.8	3580	↑	"
After 12 days Bellergal		160/110	79	65.1	5.2	2100	+	
A. B.	38							
Before		90/70	62	21.9	1.36	4700	↑	"
After 14 days Bellergal		100/75	60	34.8	2.09	3350	+	
E. H.	29							
Before		120/75	87	24.4	2.13	3660	↑	"
After 28 days Bellergal		125/75	62	70.0	4.34	1230	+	

TABLE III (CONTINUED)

NAME	AGE	B.P.	FR.	V_S	V_M	W		STATE
B. S.	25							
Before		115/90	59	29.1	1.71	5980	↑	histotropic
After 14 days Bellergal		115/90	65	31.2	2.07	3980	o	
Average								
Before		115/80	67	33.7	2.25	3745		
After treatment		118/80	65	56.8	3.51	2408		

Ps and Pd = systolic and diastolic pressures (Normal mean pressure 140/80)
V_S = stroke volume in c.c. (Normal mean = 67 c.c.)
Fr = rate/min. (Normal mean 72/min.)
V_M = minute volume in 1,000 c.c. (Normal mean = 4.6 liters)
W = peripheral resistance Dynes sec./cm.^{5} Normal average = 1,800 $\frac{\text{dynes sec.}}{\text{cm.}^5}$

*These are patients in various states of neurocirculatory asthenia. The ⟶ in the next to the last column indicates increase or lowering of circulatory values after Bellergal treatment. The + indicates improvement of subjective symptoms; o = no change in symptoms; − indicates worsening of complaints.

tients, seven "histotropic" patients, and six normal persons. Normal persons were considered to have a minute volume of 3.5 to 5.5 liters with normal peripheral resistance and a normal average pressure. We are aware that these are arbitrary criteria, but they are the result of long years of experience and are based on a series of over 500 circulatory determinations. In any case, the values observed in the extreme cases are far in excess of those of our assumed "normal values". In the "ergotropic" individuals, the previously increased stroke and minute volumes were reduced to normal and occasionally fall below normal.

In the "histotropic" individuals, the circulatory values increased in the direction of the normal levels, a tendency, however, which is not as complete as that which occurs in the "ergotropic" group. This would seem to confirm the therapeutic observation that Bellergal is relatively less effective in the "histotropic" group of patients.

The administration of Bellergal to normal individuals in long-term tests resulted in no characteristic change. A drop in stroke and minute volumes occurred in three subjects while three subjects showed increases. A comparison between short-term and long-term effects is presented in Fig. 3. It demonstrates that in the "ergotropic" individual in the short-term tests pulse wave amplitudes are lowered and the average blood pressures remain constant; in the long-term test the pulse wave amplitudes are reduced. In the "histotropic" individuals, a further depression of the circulatory state occurs in the short-term tests while in the long-term tests the majority of the cases show improvement.

DISCUSSION

In the short-term tests ergotamine tartrate works predominantly as a depressor agent in "ergotropic", "histotropic" and normal states. The exact mode of action is difficult to explain because of the complex action of this alkaloid. Ergotamine can produce: (1) a peripheral adrenergic blockade, (2) a central sedative action, (3) bradycardia, and (4) peripheral vasoconstriction. In the "ergotropic" individual, the primary action is probably one of central "sedation" on the autonomic regulative centers which leads to a decrease in stroke volume and pulse rate resulting in a secondary compensatory constriction of the peripheral vasculature. Such compensatory response is always to be considered as accompanying a change in the stroke volume. On the other hand, it is possible that the dilated peripheral vessels are constricted by the ergotamine in the "ergotropic" state; the increase in peripheral resistance would then lead reflexly to a lowering of cardiac output. The first theory is the more plausible one since in our investigation the ergotamine doses employed never showed any evidence of vasoconstriction.

In the extreme "histotropic" state, the observed increase in the minute volume after ergotamine may be explained by its adrenergic blocking effect on the constricted peripheral vessels. This apparently contradictory action of the same drug may be explained by the fact that the effect on the autonomic nervous system always takes place in the area in which the greatest deviation from the normal is present. In the "ergotropic" state, this is the case in the overactive vasomotor center, and in the "histotropic" state, it occurs in the sympathicotonically constricted peripheral vasculature.

The belladonna alkaloids in Bellafoline increase the depressed "histotropic" response and promote circulation by inhibition of the cardiac vagus. It is difficult to interpret how the inhibitory action of Bellafoline in the "ergotropic" state comes about. It may be that a depression of the vagus on the "ergotropically" dilated heart leads to a lowering of the stroke volume.

The effect of phenobarbital in the "ergotropic" state may be explained by its sedative action on the dynamogenic zones of the diencephalon.[18] In the "histotropic" state, however, the inhibitory sedative action must be directed at those areas of the diencephalon responsible for relaxation or sleep.[18] The sedative action of the barbiturate in the "ergotropic" person may explain why these drugs are of benefit to: (1) hyperthyroid patients, (2) early hypertensives, (3) patients in the initial phases of angina pectoris which, according to Schimert[9-12] is always accompanied by an "ergotropic" circulatory state.

The effect of long-term Bellergal treatment is inherent in its normalization of the "ergotropic" hyper-responsive and constricted vasculature. This depression has important consequences: the permanently elevated cardiac output, which is probably an etiologic factor in coronary insufficiency and is partially responsible for the development of certain forms of hypertension, is reduced to normal. This is accompanied by a relative drop in oxygen requirements of the

heart which in turn leads to an improvement in coronary reserve. It explains the frequent observation that Bellergal may improve anginal and hypertensive symptoms particularly in young individuals with evidence of vegetative dystonia.

SUMMARY

1. Two types of hemodynamic disturbances are observed in neurocirculatory asthenia. These per se physiologic states are pathologic only if they are not commensurate with the physiologic demands of the organism:

(a) "Ergotropic" state—hyper-responsive circulation with a high stroke and minute volume, lowered peripheral resistance and a tendency toward hypertension.

(b) "Histotropic" state—reduced circulation with a low stroke and minute volume and a tendency to hypotension.

2. It has been shown that Bellergal, a combination of Bellafoline, ergotamine tartrate, and phenobarbital may normalize both types of circulatory dystonia.

3. Ergotamine tartrate intravenously depresses the circulation in the "ergotropic" and normal individual and increases circulation only in the extreme "histotropic" patient.

4. Bellafoline intravenously increases the "histotropically" depressed circulation and depresses the "ergotropically" elevated circulation.

5. Phenobarbital intravenously depresses the "ergotropic" circulation and may in some "histotropic" cases raise the stroke and minute volume.

6. The combination of these three substances (intravenously) in "ergotropic" and normal states leads to a drop in stroke and minute volumes. An increase in circulatory values occurs in some "histotropic" individuals.

7. Bellergal by mouth normalizes the "ergotropic" state as well as the "histotropic" circulatory state after several days of administration.

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VENTRICULAR FIBRILLATION ELICITED BY FOCAL COOLING

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THE sudden and unexpected appearance of ventricular fibrillation during experimental procedures on the dog's heart is well known. Often, all that is required for its production is to touch the heart in situ with an instrument; in other instances ventricular fibrillation sets in when the heart comes in contact with the sharp edge of a resected rib.[14] It is assumed that this phenomenon is due to a premature beat elicited mechanically during the "vulnerable phase".[25] In particular, we have had the impression for many years that contact between the heart and a cold instrument causes ventricular fibrillation.

In a series of experiments performed in this laboratory, the sinus node was clamped off and auricular flutter or fibrillation was produced by topical application of Acetylcholine. These arrhythmias were immediately abolished by cooling of the atrioventricular node and reappeared on removal of the cooling thermode. This permits the conclusion that auricular flutter and fibrillation may originate by rapid firing of stimuli in the atrioventricular node alone.[17] Cooling of the atrioventricular node was accomplished by lifting the heart from its pericardial bed and applying the thermode to the area of the atrioventricular node through the vena cava inferior or the coronary sinus vein. During this procedure the thermode frequently touched the ventricle and occasionally, in the course of prolonged cooling, ventricular fibrillation appeared. This led us to investigate the effect of cooling a small area of the ventricle, during rapid ventricular activity caused by auricular flutter or auricular fibrillation.

METHOD

All the experiments were performed on dogs anesthetized with Nembutal given intraperitoneally. The dose was approximately 1 c.c. per 5 pounds. After artificial respiration had been instituted, the sternum and adjacent portions of the ribs were resected and the pericardium was opened. In these experiments, the vagi were severed in the neck and the electrocardiogram was registered in Lead II (unless otherwise stated in Table I).

The cooling was done with a test tube filled with ice, and the area cooled was about one square centimeter. The thermode was applied with just enough pressure to maintain contact with the heart. In most experiments the area

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TABLE I

DATE	PREVAILING RHYTHM	ELICITED BY	VENTRICLE COOLED	RESULT	DURATION OF COOLING IN SECONDS	REMARKS
3/17	flutter	aconitine	right	ventr. fibr.	74.20	
3/24	fibrill.	aconitine	left	ventr. fibr.	72.60	
3/31	flutter	aconitine	right	sinus rhythm	136.00	Cooling repeated after 5 minutes
3/31	flutter	aconitine	right	ventr. fibr.	113.20	
4/ 7	flutter	aconitine	right	ventr. fibr.	41.60	
4/14	flutter	aconitine	right	sinus rhythm	135.20	Extrasystoles after 70.60 seconds
4/14	flutter	aconitine	right	sinus rhythm	139.40	Extrasystoles after 38.40 seconds
4/14	flutter	aconitine	left	ventr. fibr.	97.40	Extrasystoles after 56.00 seconds
4/21	flutter	aconitine	right	sinus rhythm	106.00	Cooling repeated after 7 minutes
4/21	flutter	aconitine	right	ventr. fibr.	110.20	
4/28	flutter	aconitine	right	ventr. fibr.	41.60	
5/ 5	flutter	faradization	right	ventr. fibr.	51.00	
5/12	fibrillat.	aconitine	right	sinus rhythm	26.20	
5/12	fibrillat.	aconitine	right	ventr. fibr.	34.40	
5/19	sinus rhythm	0	right	sinus rhythm	84.20	Cooling repeated after 5 minutes
5/19	flutter	aconitine	right	ventr. fibr.	36.20	
5/26	sinus rhythm	0	right	sinus rhythm	470.00	Vagi not severed; first extrasystoles after 220.00 ventricular fibrillation after cessation of cooling
6/ 2	sinus rhythm	0	right	sinus rhythm	48.00	Extrasystoles after 38.00 seconds; vagi not severed; Lead III
6/ 2	sinus rhythm	0	right	sinus rhythm	64.00	
6/ 2	flutter	faradization	right	ventr. fibr.	6.80	
6/ 9	sinus rhythm	0	right	sinus rhythm	186.00	Vagi not severed; first ventricular extrasystoles after 70.40 seconds; first ventricular extrasystoles after 102.60 seconds
6/ 9	sinus rhythm	0	right	sinus rhythm	111.60	
6/ 9	ventr. tachycardia	aconitine	right	ventr. fibr.	35.80	
6/16	ventr. extrasystoles	aconitine	right	ventr. fibr.	136.00	

cooled was located approximately in the center of the right ventricular surface, away from the "central region" near the coronary sulcus. In the experiments in which the left ventricle was cooled, the thermode was applied at the left cardiac border, slightly posteriorly and above the apical area.

Persistent auricular fibrillation was induced in some experiments by faradic stimulation of the auricles or, when this method was unsuccessful, by the application of a few crystals of aconitine on the surface of the right auricular appendage. In all experiments the electrocardiogram was taken continuously from the beginning of the cooling to a few seconds after its termination.

RESULTS

The results are shown in Table I and in Figs. 1 to 8.

Cooling of the ventricle, as described above, during auricular flutter or fibrillation, led within a short time to the appearance of ventricular fibrillation (Fig. 1). In some experiments ventricular fibrillation occurred only after the second or third trial of cooling. The shortest cooling time necessary to elicit ventricular fibrillation during auricular flutter or fibrillation was 6.8 seconds (Fig. 5); the longest was 113.2 seconds.

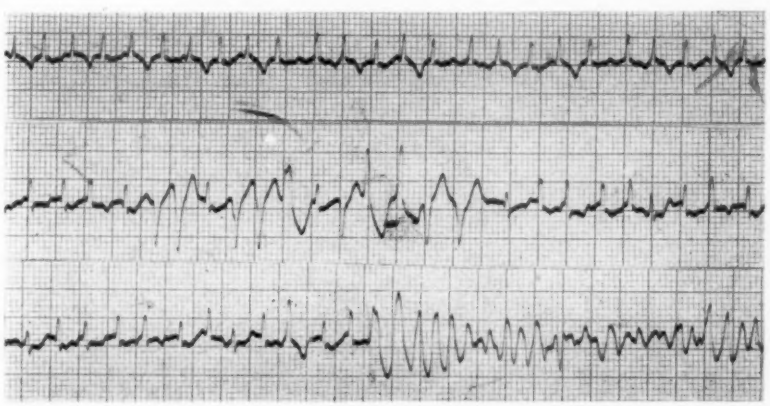

Fig. 1.—Experiment of April 7. *A*, shows an aconitine-induced auricular flutter with irregular atrioventricular block just before the cooling. *B* and *C* are continuous. *B* shows the first extrasystoles during the cooling originating in both ventricles. *C* shows ventricular fibrillation which started a few seconds later.

No electrocardiographic changes were observed at the beginning of the cooling. The absence of electrocardiographic changes involving the RS-T segments and T waves is not surprising, since it is known that any damage, even burning of the anterior wall of the heart, particularly if the injured area is not in contact with conducting tissue, will not alter the electrocardiogram in the standard leads.

After a variable length of time, two changes occurred suddenly and simultaneously and persisted until the end of the cooling. The cooled portion of the ventricular muscle which had retained a normal tonus became softer and flabby, and pressure on the thermode had to be decreased in order to avoid indenting

the ventricular wall. At the same time, the electrocardiogram showed a depression of the RS-T segment (Fig. 2). In most experiments extrasystoles originating in the cooled and the other ventricle appeared at this time and increased in number, leading soon to ventricular fibrillation, while in some experiments fibrillation set in without warning.

In several experiments, after the described changes in tonus and in the electrocardiogram, the auricular arrhythmia stopped and was replaced by a slow sinus rhythm (Figs. 2, 3, and 7). The sinus rhythm was often irregular (Fig. 3) and shifting of the pacemaker occurred (Fig. 7). In the experiment of April 14 (Fig. 3) the first two coolings abolished auricular flutter while the third cooling induced ventricular fibrillation. These effects could not be predicted.

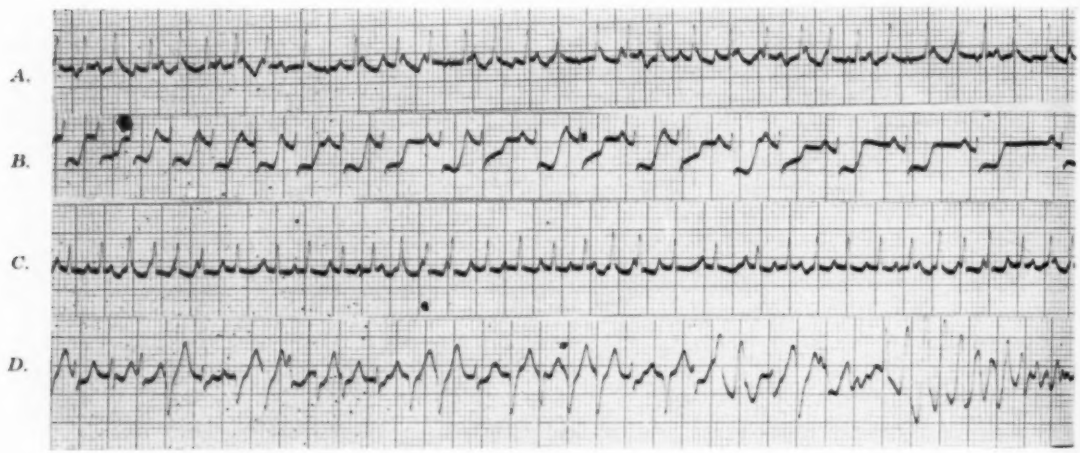

Fig. 2.—Experiment of March 31. *A* shows an aconitine-induced auricular flutter just before the cooling. Cooling of the right ventricle changed the flutter to sinus rhythm within 136 seconds. *B* shows the electrocardiogram at the end of the cooling demonstrating the change from flutter to sinus rhythm and the depression of the RS-T segments. *C* obtained 5 minutes later, shows again flutter just before the second cooling. *D* demonstrates the onset of ventricular fibrillation after 113 seconds of cooling and also shows the extrasystolic arrhythmia preceding the fibrillation.

The disappearance of auricular flutter or fibrillation during focal cooling of the ventricle was not fortuitous; it was observed in aconitine-induced arrhythmias of the auricles and these arrhythmias otherwise will persist without change for more than one hour. Furthermore, in all experiments in which the cooling the ventricle abolished an auricular arrhythmia, the arrhythmia reappeared within 2 to 3 seconds after removal of the thermode. The interval between periods of cooling was always long enough so that one cooling could not be influenced by the previous one.

Occasionally there was also a disturbance of the atrioventricular conduction as a consequence of the cooling (Figs. 3 and 4). With regard to the effect of cooling no differences were noted between auricular flutter or fibrillation due to aconitine, and that due to faradization (Fig. 4).

In our experiments up to the present, ventricular fibrillation did not occur during the cooling when this was performed during an undisturbed sinus rhythm.

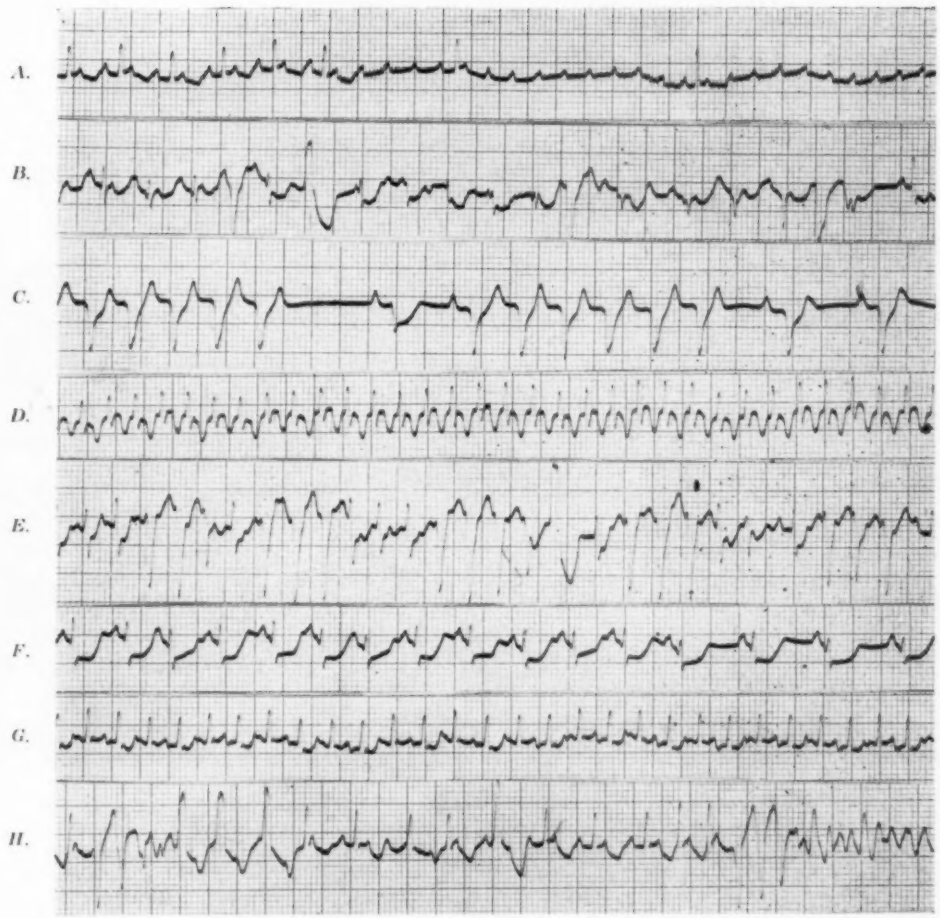

Fig. 3.—Experiment of April 14. *A* demonstrates aconitine-induced flutter and the effect of faradic stimulation of the right vagus nerve in the neck. The flutter rate increases from 300 to 375. Cooling of a small area of the right ventricle elicits extrasystoles which appeared almost simultaneously with a depression of the RS-T segment *B*; shortly afterward, sinus rhythm is present with a prolongation of the P-R interval to 0.18 second, 135.2 seconds after cooling was begun *C*. *D* demonstrates flutter at the onset of the second attempt of cooling of the right ventricle. Cooling this time elicited ventricular extrasystoles after 38.4 seconds *E* and later abolished the auricular flutter while simultaneously there appeared a marked depression of the RS-T segment after 139.4 seconds *F*. The strip in *G* again shows flutter about 4 minutes later, which had actually appeared a few seconds after cooling was stopped. Cooling an area of the left ventricle elicited ventricular fibrillation within 97.4 seconds *H*.

However, multifocal ventricular extrasystoles as well as slowing of the existing sinus rhythm were frequently seen (Fig. 5) and in one instance discontinuation of the cooling was quickly followed by a burst of ventricular extrasystoles and ventricular fibrillation (Fig. 6). In another experiment (Fig. 8) in which cooling was performed during sinus rhythm with ventricular extrasystoles the appearance of ventricular fibrillation was observed during the cooling. It is most probable that in a larger series of experiments, ventricular fibrillation will occasionally be observed while cooling is applied during a regular sinus rhythm.

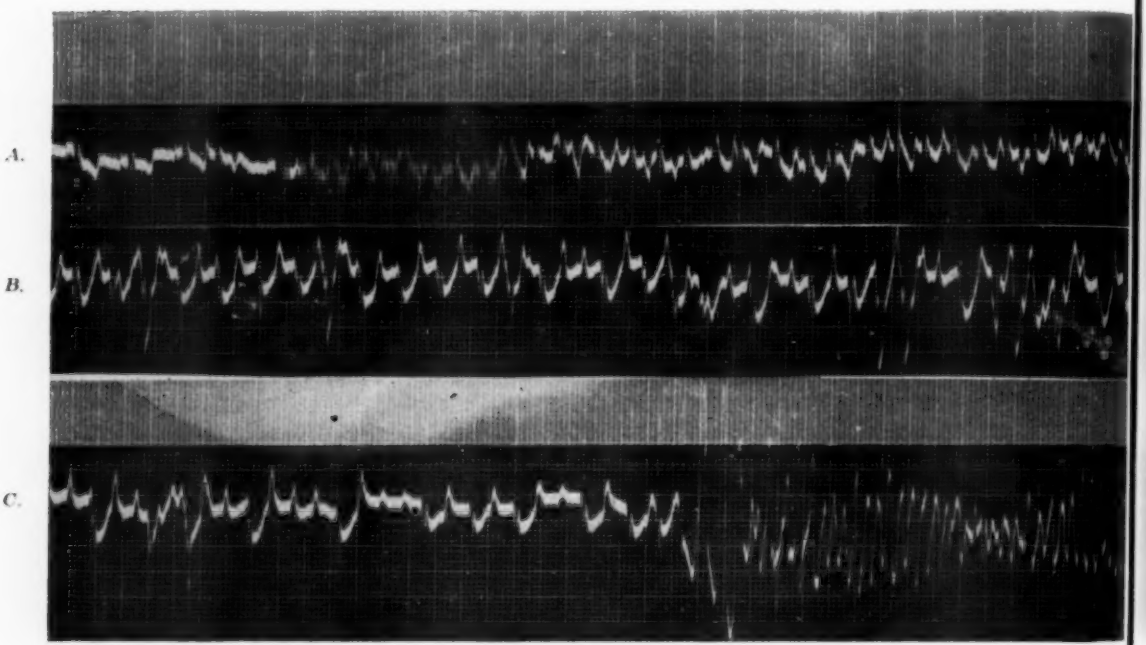

Fig. 4.—Experiment of May 5. *A* **reveals sinus rhythm followed by auricular flutter elicited by faradic stimulation of the right auricle. In** *B* **the first extrasystoles and the changes of the RS-T segments appear during the cooling. A few seconds later** *C* **was obtained; there are more extrasystoles, disturbance of atrioventricular conduction appears and suddenly ventricular fibrillation sets in.**

In many instances the ventricular fibrillation exhibited at first a series of regular ectopic beats in succession (Figs. 4, 7, and 8) showing a gradual increase of rate, before the characteristic irregularity of the waves appeared; this "initial tachysystolic phenomenon"[24] lasted often longer in these experiments than in other forms of ventricular fibrillation.

DISCUSSION

The above experiments demonstrate the production of ventricular fibrillation by focal ventricular cooling during rapid ventricular activity. In this series, the shortest cooling time was 6.8 seconds and the longest 113.2 seconds. Where fibrillation did not occur during the first attempt, it could always be observed after the second or third attempt. No differences were noted whether the auricular flutter or fibrillation was due to faradization or to focal application of

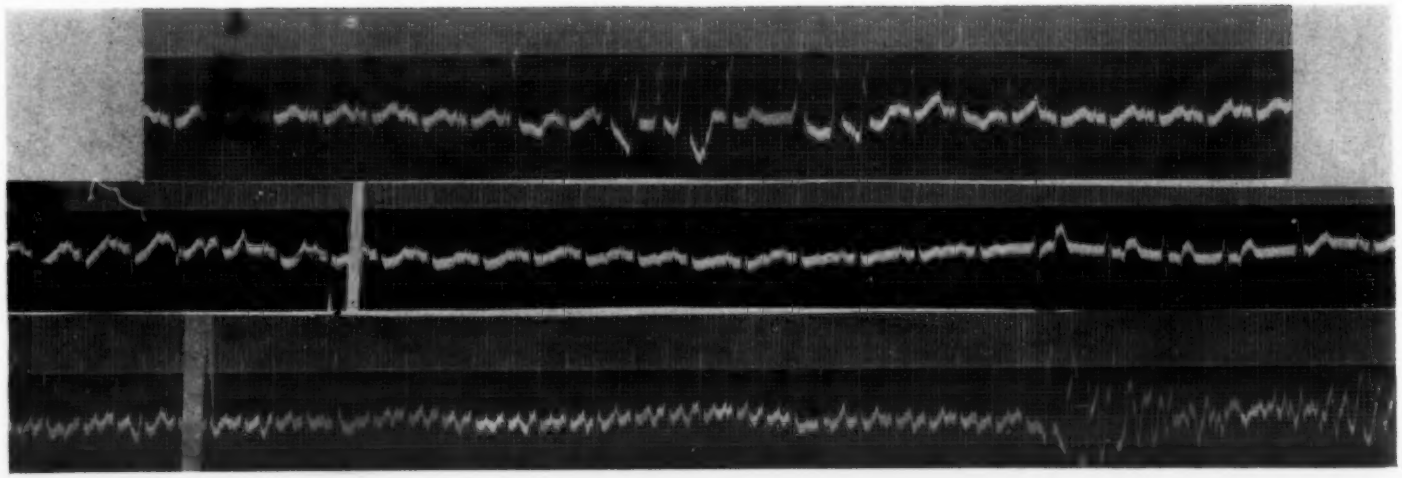

Fig. 5.—Experiment of June 2. Two attempts of cooling during sinus rhythm in the first instance led (top tracing) only to a burst of extrasystoles, and in the second trial (middle tracing) to ectopic ventricular beats with reversed conduction to the auricles after the cooling is discontinued (vertical white line is a signal). Cooling during auricular flutter (third strip) beginning with the vertical white line (signal) elicited ventricular fibrillation within 6.8 seconds.

aconitine. In one experiment in which sinus rhythm prevailed fibrillation occurred 4.2 seconds after the cooling thermode had been removed. In another experiment in which ventricular ectopic beats existed during sinus rhythm cooling also caused ventricular fibrillation.

In some cases, local cooling of a ventricle led to a remarkable effect on the auricles. Auricular flutter (or fibrillation) was abolished and a sinus rhythm was observed. This lasted only a few seconds longer than the cooling. There was a marked slowing of the heart when sinus rhythm appeared.

The effect of cooling of the heart on fibrillation has been studied only in a few instances. McWilliam mentions the possibility of arresting ventricular fibrillation by cooling of the whole heart,[14] and his results were confirmed.[2,15] Conversely, sudden cooling of the ventricles, particularly cooling of a branch of the coronary artery produced fibrillation.[11] Langendorff, however, repeating

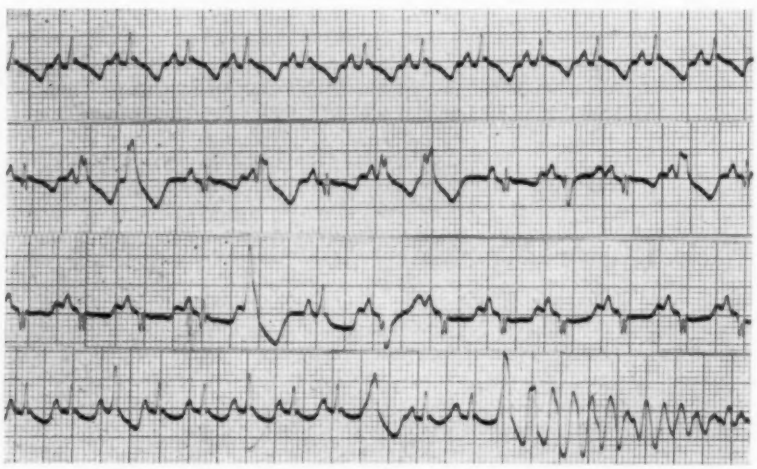

Fig. 6.—Experiment of May 26. *A* shows a sinus rhythm before the cooling. *B* demonstrates the first ventricular extrasystoles 220 seconds after cooling was begun. *C* shows the electrocardiogram at the end of cooling with the marked depression of the RS-T segments. *D* shows the beginning of ventricular fibrillation a few seconds after the cooling ended.

these experiments did not obtain fibrillation in spite of extending the duration of the cooling to 15 minutes.[12] Cooling of dogs to 30 to 37° C. has been tried as a prophylactic measure to avoid fibrillation, but without success.[25] Hoff and Stansfield examined the effect of local cooling of the heart of the dog in an attempt to explain the phenomenon of the vulnerable period.[9] Local cooling facilitated multiple response and the appearance of ventricular fibrillation if single induction shocks were applied early in diastole to a noncooled region. The multiple response and the fibrillation originated in the cooled area. Taylor and and his associates[22] performed experiments on dogs in which they created myocardial injury by focal cooling. In eighty-two dogs the authors obtained ventricular fibrillation or cardiac standstill twenty-one times. These changes of the cardiac mechanism were not investigated. Experimental intracardiac surgery during general hypothermia is attended by a high incidence of ventricular fibrillation.[1,15]

The effect of cooling on nerves has been extensively studied particularly with reference to the firing of impulses. Since work with heart muscle involves tissue possessing many physiologic properties of nervous tissue, certain conclusions may be drawn from the experiences of neurophysiologists.

The changes in nerve produced as a consequence of cooling are a slowing of chemical reactions, increased excitability to electrical stimulation,[4,19] and the diminution or even elimination of accommodation.[19,20] One theory is that owing to accommodation a continuous current causes only one response: the firing of one impulse in the medullated nerve. Without accommodation, every continuous stimulus above threshold would cause rhythmic firing of impulses at a frequency determined only by the duration of the refractory phase. It has been

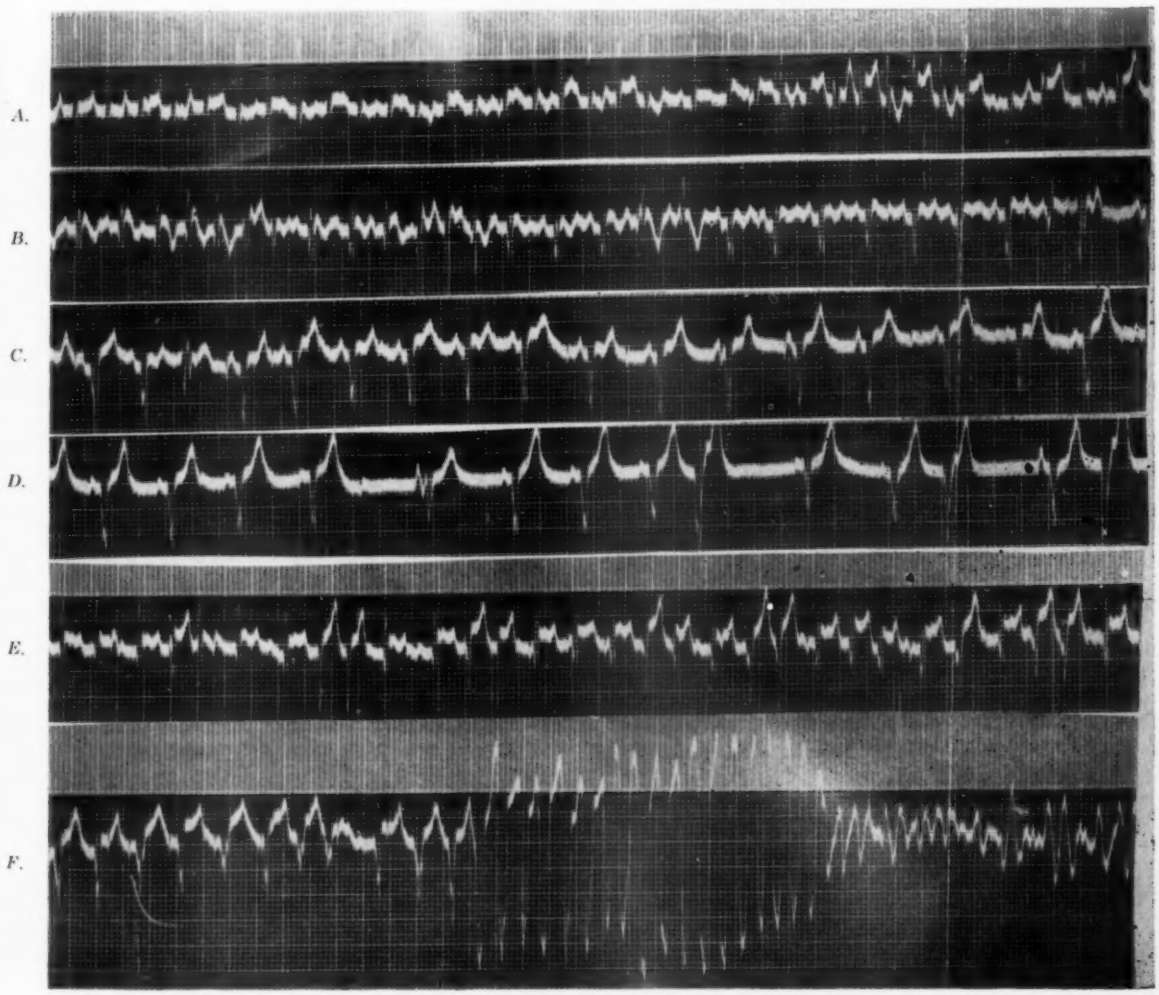

Fig. 7.—Experiment of May 12. *A* shows auricular fibrillation and was registered before the cooling. *B, C, D* are continuous and show the reversion of fibrillation into a very slow and irregular sinus rhythm with ectopic beats. *E* and *F* are again continuous and show the appearance of ventricular fibrillation during the second period of cooling.

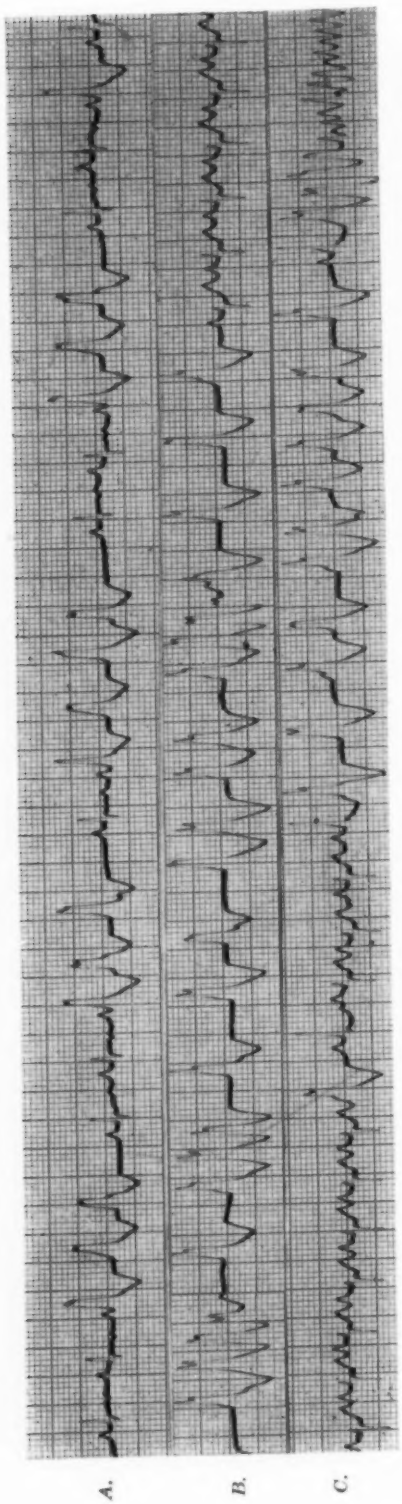

Fig. 8.—Experiment of June 16. Focal application of Veratrin on the conus of the right ventricle had caused parasystole. Twenty minutes later this arrythmia almost disappeared (*A*). The cooling began 4.3 seconds after the beginning of *A*. Later the ectopic beats disappeared but groups of extrasystoles interrupted the sinus rhythm (*B*, obtained about 95 seconds after the onset of the cooling). The last burst of extrasystoles, in which the ectopic beats appeared with increasing frequency, reached a critical rate and ventricular fibrillation followed (*C*).

shown that rhythmically active organs have very poor accommodation.[16] Frog nerves, which generally have good accommodation, show slow accommodation upon cooling and exhibit repetitive response when stimulated by a constant current.[10] The same effect is present when the concentration of calcium is decreased.[21] The rheobase falls with a lowering of the temperature[20] and cooling prolongs the duration of chronaxie.[3] The positive afterpotential coinciding with the subnormal phase is reduced.[5,6] During cooling of one portion of a nerve a difference in potential develops between the cooled and non-cooled parts, the warmer part being positive with relation to the cooler one.[23]

Reflexes are augmented during cooling[8] and new reflexes may appear which were not present at normal temperatures. Of great interest in regard to our results are experiments performed on the artificial synapse[7] in which a sudden drop in temperature increased the transmitted response. Cold has an "enormous" effect in facilitating transmission from sensory to motor fibers, enhancing the appearance of rhythmic oscillations and increased excitability.

The difference in potential between the cooled and noncooled areas may be of sufficient magnitude to excite and to allow repetitive responses particularly since the rheobase of the cooled area is decreased and its faculty of repetitive response is greater. Thus appearance of extrasystoles upon cooling a part of the ventricle can be explained. The repetitive rapid firing of one center leads to firing of impulses (extrasystoles) of other centers provided this occurs at a certain rate above a critical level;[18] the activity of many sustaining centers causes ventricular fibrillation. The enhancing of the appearance of ventricular fibrillation during cooling by the presence of rapid ventricular activity as shown in these experiments with auricular flutter and fibrillation is thus easily understood. During sinus rhythm focal cooling causes ventricular fibrillation only if bursts of ventricular extrasystoles appear with a sufficiently high rate.

The concomitant effects of ventricular cooling upon the auricles and the atrioventricular conduction are noteworthy. These are the transient disappearance of flutter and fibrillation, slowing and irregularity of the sinus rhythm and partial atrioventricular block. These phenomena were observed repeatedly with both vagi severed in the neck (Table I). Several explanations are possible but no attempt will be made to discuss them until further data are obtained.

The observations of McWilliam are pertinent to these studies and will be cited in full: "I have on some occasions observed phenomena of the same kind (fibrillation) when an animal (cat) was suddenly and powerfully cooled by the application of a mixture of ice and salt to the surface of the skin and the insertion of an ice bag into the abdominal cavity. After the cooling had gone on for a time, the ventricles suddenly passed into a state of fibrillatory contraction."[14] These observations show that the effect of cooling other areas of the body may influence cardiac activity. Investigations of this phenomenon are in progress.

The sudden change of the muscular tonus during the cooling which appeared shortly before the change in the rhythm is in all probability connected with the electrical alterations discussed above. The fact that the electrocardiographic depression of RS-T appeared simultaneously with the change in tonus indicates

that a profound disturbance of other parts of the ventricles occurs at this time, since damage to the anterior surface of the heart from burning, mechanical irritation, etc., is not sufficient to alter the electrocardiogram in the standard leads. In favor of this interpretation there is also the fact that the ventricular extrasystoles which appeared at that time did not originate only in the cooled area; often they came from the other ventricle.

In view of the increasing frequency with which cardiac surgery is performed, of the recent recommendation to operate after induction of a general hypothermia, and of the fairly common reports of ventricular fibrillation in the course of such operations, we decided to publish the results of our experiments. After analysis of the mechanism of the fibrillation elicited by cold, studies will be undertaken designed to prevent this dramatic event.

SUMMARY AND CONCLUSIONS

Cooling of a small area of the right or left ventricle of the exposed heart of a dog during the presence of a rapid ventricular activity (auricular flutter or fibrillation) leads to ventricular fibrillation. This event is often observed at the first attempt or during the second or third performance of the cooling. In one experiment ventricular fibrillation appeared after only 6.8 seconds of cooling. The fibrillation is preceded by extrasystoles, originating in the cooled and in the contralateral ventricle.

Cooling during the presence of sinus rhythm elicited usually bursts of ventricular extrasystoles; in one experiment ventricular fibrillation appeared a few seconds after cooling was discontinued. In another experiment in which ventricular extrasystoles were present their number increased during the cooling and ventricular fibrillation appeared.

Focal cooling of the ventricles had astonishing effects on the activity of the auricles. Auricular flutter or fibrillation, caused by aconitine application, changed into sinus rhythm; cessation of cooling led to reappearance of these auricular arrhythmias within 2 to 3 seconds. Sinus arrhythmias also appeared and atrioventricular conduction disturbances were observed.

The pertinent literature is discussed and an attempt is made to show possibilities of an explanation of the observed phenomena on the basis of the effect of cold on the excitability and on the firing of impulses of nerves.

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PRELIMINARY OBSERVATIONS OF RAUWILOID*-HEXAMETHONIUM† COMBINED THERAPY OF HYPERTENSION

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RAUWILOID[1] and other preparations of Rauwolfia serpentina[2] are of value in the clinical management of the patient with mild hypertension without complications. No serious untoward side reactions have been observed and in addition to moderate blood pressure reduction its administration usually produces certain desirable effects such as a sense of well-being and mild sedation without somnolence. The latter response also makes it useful in the preparation and stabilization of patients with severe hypertension prior to administering more potent hypotensive agents. The purpose of this paper is to report the preliminary observations of the use of combined Rauwiloid-hexamethonium therapy in the treatment of hypertension and to suggest a tentative approach to the therapy of this disease.

METHODS AND MATERIALS

Twelve of the patients used in this study are from the office practice of the authors and thirteen from the Veterans Administration Hospital. All of the patients were unselected and have been followed as outpatients. The pertinent clinical data prior to treatment are summarized in Table I, and the control blood pressures are tabulated in Table III. It is obvious that the severity of the hypertension was variable from patient to patient and that the group as a whole presents a fair cross section of the disease.

Nineteen of the patients were first given oral hexamethonium according to the titration procedure previously described[3]. This consisted of starting on small doses (250 mg. four times a day) and then progressively increasing the dose in an incremental fashion until an optimal response was obtained. Most of the nineteen patients who were first treated with hexamethonium were observed for six months or longer prior to the addition of Rauwiloid. When Rauwiloid was added it was also started in small doses (2 mg. four times a day‡) and the dose was progressively increased in an incremental fashion. The dose was

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*Supplied by Riker Laboratories, Inc., Los Angeles, Calif., as "Riker-1043" and "Riker-1070" and now available as "Rauwiloid" which is an extract of Rauwolfia serpentina.

†Supplied through the courtesy of Burroughs Wellcome & Co., Inc., as Hexameton; Ciba Pharmaceuticals, Inc., as Esomid; Warner-Chilcott Laboratories as Methium Chloride.

‡Dosages of the original preparations (designated Experimental Preparation #1070 and #1043) were expressed in terms of their crude root content. The dose of Rauwiloid, as presently available, is expressed in terms of the alkaloidal content, i.e., each tablet contains 2 mg. of the alkaloids. This represents the therapeutic activity found in approximately 125 mg. of the crude root.

maintained at 32.0 mg. daily in most cases, although current data would seem to indicate that 8 to 12 mg. (4 to 6 tablets) per day is adequate and that very little additional hypotensive effect is produced by the larger dose. When Rauwiloid was used as the initial drug (six patients), a period of at least three months elapsed before hexamethonium was added to the therapeutic regimen, thus allowing the observer to evaluate the hypotensive response to Rauwiloid alone. The drugs were taken four times daily (with meals and at bedtime).

TABLE I. CLINICAL SUMMARY OF PATIENTS PRIOR TO COMBINED RAUWILOID-HEXAMETHONIUM THERAPY OF HYPERTENSION

NAME	AGE	RACE	SEX	ABNORMAL ECG	COMPLICATIONS			DIAGNOSIS
					RENAL	CARDIAC	CEREBRAL	
V.D.*	71	W	F					HVD
H.U.*	50	W	F					HVD
B.R.*	55	W	M	X	X	X	X	HCVD
G.W.*	45	N	M	X	X	X		HCVD
F.S.*	37	N	M				X	HVD
B.J.*	56	N	M	X	X	X		HCVD
A.R.	52	W	M	X	X	X	X	MHCVD
J.R.	54	N	M	X	X	X	X	HCVD
W.M.	36	W	M		X			HVD
H.C.	32	W	M		X			HVD
W.A.	56	N	M					HVD
T.E.	47	N	M	X	X	X		HCVD
C.A.	43	N	M	X	X	X		HCVD
H.S.	59	W	M	X		X		HCVD
T. L.	62	W	M					HVD
B.A.	47	N	M	X	X	X	X	HCVD
B.H.	63	W	F	X	X	X		HCVD
M.W.	48	W	F	X		X		HCVD
E.W.	42	W	F	X		X		HCVD
L.I.	51	W	M	X		X		HCVD
B.A.	38	W	F					HVD
C.A.	56	W	M	X		X		HCVD
C.O.	44	W	F	X		X		MHCVD
P.R.	38	W	F					HVD
L.H.	34	W	F					HVD
Total		W-17 N-8	F-9 M-16	15	11	15	5	

*Those patients initiated with Rauwiloid and hexamethonium later added.

W—White
N—Negro
M—Male
F—Female
MHCVD—Malignant hypertensive cardiovascular disease
HCVD—Hypertensive cardiovascular disease
HVD —Hypertensive vascular disease
ECG —Electrocardiogram

Pretreatment studies included the usual clinical and laboratory data: complete blood count, urinalysis, serology, orthodiagram, electrocardiogram, fundoscopic classification (Keith-Wagener), blood urea nitrogen, phenolsulfonphthalein, and Fishberg concentration tests. These were repeated at one or two month intervals. During the titration period the patients were seen daily or semiweekly but were not hospitalized except when a critical problem presented itself or if the proper dose of the drug was particularly difficult to establish. Following the titration period the patients were seen at intervals of one to twenty-

one days depending on the clinical course. At each outpatient visit the blood pressure (recumbent and upright),* pulse rate, weight, symptoms, and a brief physical examination were recorded.

RESULTS

Clinical Response.—Nineteen patients received optimal dosages of hexamethonium prior to the administration of Rauwiloid. Faintness, constipation, and impotency (in the men) were usually observed to some degree (Table II, C_6). It was observed that a large per cent of these patients who were treated with hexamethonium alone for at least six months developed a certain degree of adjustment or tolerance to the adverse effects. When Rauwiloid was added to the regimen (C_6R), a sense of well-being was observed which was associated with increased appetite and sedation without somnolence in a significant majority of the patients. Bradycardia and nasal congestion also appeared after Rauwiloid was added to the therapeutic program. There was a reduction in the frequency

TABLE II. CLINICAL RESPONSE TO COMBINED RAUWILOID-HEXAMETHONIUM THERAPY OF HYPERTENSION

	R		RC_6		C_6		C_6R	
	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
Total treated	6	100	6	100	19	100	19	100
Sense of well-being	5	83	5	83	0	0	14	74
Nasal congestion	3	50	3	50	0	0	14	74
Bradycardia	6	100	6	100	0	0	13	68
Increased appetite	3	50	3	50	0	0	14	74
Sedation	6	100	5	83	0	0	15	79
Faintness	0	0	2	33	16	84†	10	53
Constipation	0	0	2	33	16	84†	8	42
Impotency	0	0	3	50	17	89	5	26
B.P. response*	2	33	6	100	19	100	19	100

*Drop in mean blood pressure, upright, greater than 20 mm. Hg.
R—Rauwiloid alone
RC_6—Rauwiloid supplemented by hexamethonium
C_6—Hexamethonium alone
C_6R—Hexamethonium supplemented by Rauwiloid
†Present at some time during initial therapy but decreased in frequency and intensity prior to the addition of Rauwiloid.

of complaints of faintness, constipation, and impotence. The small number of patients (6) who were initially treated with Rauwiloid can be expected to demonstrate a trend but no conclusive statements can be made. It appears, however, that the untoward side effects due to the addition of hexamethonium are ameliorated when Rauwiloid has been previously given (Table II, RC_6).

*The control blood pressure in the current report is the average of the observations during the control period. The treatment values are the averages of all observations after therapy was established and the titration period completed.

Physiologic Response.—In the six patients to whom Rauwiloid was administered initially there was a decrease in the average mean blood pressure (diastolic plus one-third of the pulse pressure) from 159 (208/134) to 137 (183/113) mm. Hg, but after hexamethonium was added there was a much greater reduction to 104 (147/83) mm. Hg. All blood pressure records in Table III are upright values to facilitate comparison with other hypotensive agents previously and concurrently studied. The blood pressure during Rauwiloid alone showed very little additional reduction when changing from the supine to the upright position, but the maximum reduction in blood pressure obtained after hexamethonium was added to the therapy was observed in the upright position. In the nineteen patients initiated with hexamethonium therapy, there was an average reduction in mean blood pressure from 150 (199/125) to 104 (136/88) mm. Hg and another slight drop to 97 (127/83) when Rauwiloid was added. There was also a decrease in pulse rate after adding Rauwiloid which was not seen when hexamethonium was given alone. The average daily dose of hexamethonium that was necessary to achieve optimal blood pressure reduction was 2.6 Gm. when hexamethonium was used alone. In the small group of patients who first received Rauwiloid, the dose of hexamethonium was 2.3 Gm. per day. When the hexamethonium was supplemented by Rauwiloid, in a larger group of patients, the dose could be reduced to 1.7 Gm. per day. Of the twenty-five patients treated, in the current study, twenty (80 per cent) became normotensive during combined Rauwiloid-hexamethonium therapy and 25 (100 per cent) had a decrease in mean blood pressure of at least 20 mm. Hg (Table IV).

DISCUSSION

The treatment of essential hypertension remains somewhat empirical, since the etiology of the disease is not known, but the availability of potent hypotensive drugs obligates the clinician to a more determined stand in his attempt to control the disease and its complications. If this is to be done effectively, it is necessary for the physician to understand the pharmacology of the available drugs which are useful for this purpose and to choose the agent which is appropriate for the type of disease being treated. Rauwiloid when given as the only hypotensive agent has been found to be of benefit in mild hypertensives without complications. This drug by contrast to most currently available hypotensive agents presented no serious untoward side effects.[1] However, it was not effective in reducing the blood pressure in the patient with severe hypertension with complications, although it did produce symptomatic improvement through increased appetite, mild sedation, and a sense of well-being. The comparative effectiveness of many of the more potent agents has been summarized by Miller and associates.[4] At that time it seemed that hexamethonium, alone or in combination with Apresoline, was the agent of choice in the treatment of severe essential hypertension. However, the difficulties in the use of these more potent hypotensive agents such as hexamethonium cannot be ignored. Thus, it was reasoned that perhaps any collateral agent which increases the hypotensive effectiveness but decreases the side reactions of the more potent agents is worthy of clinical trial.

TABLE III. PHYSIOLOGIC RESPONSE TO COMBINED THERAPY

	PT.	DAILY DOSE C_6	MBP			CONTROL		R		RC_6		PULSE			DAILY DOSE RAUWILOID (MG.)
			C	R	RC_6	S	D	S	D	S	D	C	R	RC_6	
	G.W.*	2.5	160	150	123	200	140	210	120	170	100	72	68	80	32.0
	F.S.*	2.5	160	117	113	200	140	130	110	160	90	76	72	80	32.0
	B.J.*	2.5	167	157	123	220	140	210	130	170	100	80	68	76	32.0
	V.D.*	0.75	129	83	84	178	104	128	60	128	62	80	74	72	24.0
	H.U.*	2.5	151	136	87	208	122	188	110	120	70	88	80	84	24.0
	B.R.*	3.0	187	176	95	240	160	232	148	134	76	80	78	72	24.0
	Mean	2.3	159	137	104	208	134	183	113	147	83	79	73	77	28.0

	PT.	DAILY DOSE C_6		MBP			CONTROL		C_6		C_6R		PULSE			DAILY DOSE RAUWILOID (MG.)
		C_6	C_6R	C	C_6	C_6R	S	D	S	D	S	D	C	C_6	C_6R	
Diast. 140 and above	A.R.	2.5	2.5	200	117	117	280	160	150	100	150	100	88	84	68	32.0
	A.B.	3.0	3.0	163	137	97	210	140	170	120	110	90	72	72	68	32.0
	C.O.	3.0	1.5	181	106	103	234	154	143	88	130	90	80	76	76	32.0
	Mean	2.8	2.3	181	120	106	241	151	154	103	130	93	80	77	71	32.0

Diast. 121-140	T.E.	3.0	3.0	157	103	93	210	130	130	90	120	80	86	80	80	32.0
	C.A.	3.0	2.5	157	127	83	210	130	180	100	130	60	88	84	68	32.0
	H.S.	3.5	2.5	150	117	117	190	130	150	100	150	100	84	76	72	32.0
	B.H.	2.5	1.0	157	103	100	210	130	150	80	140	80	76	72	64	32.0
	E.W.	2.5	0.5	150	93	93	190	130	120	80	120	80	76	76	68	32.0
	B.A.	3.0	1.5	149	101	98	196	126	132	86	130	82	80	80	76	32.0
	C.Ar.	1.5	0.5	151	97	100	206	124	130	80	128	86	86	86	82	32.0
	Mean	2.7	1.6	153	106	98	202	129	142	88	131	81	82	79	73	32.0
Diast. 120 and below	J.R.	2.5	1.5	147	113	113	200	120	140	100	140	100	84	76	68	32.0
	W.M.	2.5	1.0	143	110	97	190	120	130	100	110	90	84	84	72	32.0
	W.A.	3.0	2.0	147	103	100	200	120	130	90	120	90	76	76	72	32.0
	T.L.	2.0	2.0	140	93	105	180	120	120	80	134	90	80	76	56	32.0
	M.W.	3.0	2.0	133	90	90	180	110	130	70	130	70	76	72	72	32.0
	L.I.	1.0	1.0	139	97	89	192	112	130	80	120	74	82	78	76	32.0
	P.R.	3.5	3.5	135	97	93	168	118	130	80	126	76	78	76	70	32.0
	L.H.	2.0	1.0	117	88	83	150	100	115	75	110	70	84	80	72	16.0
	H.C.	2.0	0.5	133	80	83	180	110	100	70	110	70	84	80	66	32.0
	Mean	2.4	1.6	137	97	95	182	114	125	83	122	81	81	78	69	30.2
Grand Mean		2.6	1.7	150	104	98	199	125	136	88	127	83	81	78	71	31.2

*Patients initiated with Rauwiloid and hexamethonium added later.
MBP—Mean Blood Pressure = diastolic plus one-third of the pulse pressure.
C—Control observations.
R—Observations after Rauwiloid administration.
C_6—Observations after hexamethonium administration.
RC_6—Observations after Rauwiloid plus hexamethonium.
C_6R—Observations after hexamethonium plus Rauwiloid.
S—Systolic.
D—Diastolic.

TABLE IV. COMPARISON OF BLOOD PRESSURE RESPONSE OF RAUWILOID-HEXAMETHONIUM COMBINED THERAPY WITH OTHER HYPOTENSIVE DRUGS*

	NO. PTS. TREATED	NORMOTENSIVE†		DECREASE MBP >40 MM. HG		DECREASE MBP 30-40 MM. HG		DECREASE MBP 20-30 MM. HG		DECREASE MBP 20 MM. HG	
		NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
Rauwiloid—Hexamethonium											
Group 1‡	7	3	43	6	86	1	14	0	0	7	100
Group 2	8	7	88	7	88	1	13	0	0	8	100
Group 3	10	10	100	7	70	3	30	0	0	10	100
Total	25	20	80	20	80	5	20	0	0	25	100
Rauwiloid (alone)											
Group 1‡	12	0	0	2	17	1	8	0	0	3	25
Group 2	16	3	19	2	13	2	13	2	13	6	38
Group 3	14	6	43	0	0	5	36	3	21	8	57
Total	42	9	21	4	10	8	19	5	12	17	40
Hexamethonium (alone)											
Group 1‡	16	5	31	10	63	2	13	1	6	13	81
Group 2	27	13	48	15	56	6	22	1	4	22	81
Group 3	15	10	67	1	7	7	47	4	27	12	80
Total	58	28	48	26	45	15	26	6	10	47	81
Dibenzyline (mean for 3 groups)	32	14	44	15	47	3	9	3	9	21	66
Regitine "	24	—	—	—	—	2	8	2	8	4	17
Anatensol "	31	1	3	1	3	3	10	2	6	6	19
Veriloid "	30	2	7	6	20	2	7	7	23	15	50
Apresoline "	52	5	10	5	10	4	8	8	15	17	33

*Upright blood pressure.
‡Group 1—patients whose control diastolic pressure is 140 or greater.
Group 2—patients whose control diastolic pressure is 120-139.
Group 3—patients whose control diastolic pressure is less than 120.
†Blood pressure less than 150/100 mm. Hg in upright position.
MBP—Mean blood pressure = diastolic plus one-third of the pulse pressure.

Hexamethonium and Rauwiloid together can be used concurrently with more beneficial responses and less untoward effects.

From the data presented in this study, it appears that combined Rauwiloid-hexamethonium therapy is followed by a greater degree of blood pressure reduction than with any single drug studied (Table IV). However, observations from the hypertensive clinic in the City-County Hospital were not available for the current study as they were when the statistics were collected on the effectiveness of the other drugs which are presented in Table IV. None the less, with combined Rauwiloid-hexamethonium (present report) therapy one-hundred per cent of all patients treated demonstrated a significant (MBP reduced more than 20 mm. Hg) reduction of blood pressure and 80 per cent became normotensive. When the results with hexamethonium alone[3] were evaluated in a larger previous study, only 81 per cent of the cases tolerated adequate doses to produce a significant reduction in flood pressure and only 47 per cent became normotensive. Furthermore, when Rauwiloid was used there was a reduction in the severity and frequency of the untoward side effects which accompanied hexamethonium alone, especially constipation and faintness, while the beneficial side effects due to Rauwiloid persisted; namely, increased appetite, sense of well-being, and sedation without somnolence. When Rauwiloid was added it was also possible to reduce the dose of hexamethonium to almost one-half that previously required. Furthermore, the blood pressure appeared to be more stable. This may be illustrated by two typical case histories.

M. S. C., a 41-year-old housewife was started on hexamethonium orally in March, 1952, because of progressive hypertension (blood pressure 240/140 mm. Hg) with Grade 4 fundi (according to the Keith-Wagener classification), headaches, and blurred vision. She was fairly well controlled on 3 to 3.5 Gm. of hexamethonium daily but the blood pressure fluctuated widely (from 130/80 to 200/130 mm. Hg) in a 24-hour period. Constipation and faintness were also distressing complaints. In November, 1952, after six months of fair blood pressure regulation and marked improvement of her fundi, relief from headaches and absence of blurred vision, Rauwiloid was added and the dose increased progressively to a daily dose of 32 mg. After two months of the combined hexamethonium-Rauwiloid therapy, the daily requirement for hexamethonium was only 1.25 to 1.75 Gm.; the blood pressure did not fluctuate nearly so widely (130/90 to 160/100 mm. Hg), and spells of faintness had decreased. Constipation was completely alleviated.

A. M. C., a 55-year-old insurance executive with ten years of hypertension and a pretreatment pressure of 240/160 mm. Hg was essentially asymptomatic, although there was moderate left ventricular hypertrophy. Hexamethonium was started in July, 1952, and the blood pressure reduced (on a dose of 250 mg. four times a day) to a blood pressure range of 130/90 to 200/125 mm. Hg. Rauwiloid was started in November, 1952, and by February, 1953, the total daily dose of hexamethoinum was 500 to 750 mg., and the blood pressure varied from 100/70 to 160/110 mm. Hg. Only rarely was faintness or constipation a problem at this time and the new sense of well-being was indeed welcomed.

The pharmacologic basis for the effects of combined Rauwiloid-hexamethonium therapy is not entirely clear at this time although animal studies with pure alkaloids of Rauwolfia serpentina are in progress. Nevertheless, it appears that the peripheral ganglionic blocking effect of hexamethonium acts very nicely in synergism with an apparent central vasodepressor action of Rauwiloid, both together producing better hemodynamic stability and blood pressure reduction

than when either one is used alone. The apparent stimulating effect of Rauwiloid on intestinal motility seems to act in antagonism to the parasympathetic ganglionic blocking action of hexamethonium which depresses motility. As a result the problem of constipation which is so prominent with hexamethonium alone is less likely to occur on combined Rauwiloid-hexamethonium therapy. The sedative effect of Rauwiloid is also a great asset. It is superior to phenobarbital in its ability to decrease anxiety and improve the general sense of well-being yet it has very little soporific effect.

The larger doses of Rauwiloid used in the current study are considerably greater than those recommended for routine clinical therapy. In the latter instance, at least 4 tablets (2 mg. per tablet as available on the market) should be administered per day. In our experience maximum effectiveness is not obtained with doses less than this. The larger doses employed in the current study were used in an effort to establish the maximum hypotensive effect that could be expected by using Rauwiloid for the treatment of all grades of essential hypertension. Although the optimum dose has not been established as yet, it appears that very little additional benefit is gained by using more than six to eight 2 mg. tablets of Rauwiloid every twenty-four hours.

In conclusion, while we maintain an attitude of watchful waiting for the definitive pathogenesis and rational therapy of essential hypertension, we must not overlook the therapeutic tools now available which may improve the prognosis and delay the progress of hypertensive complications. In our opinion the current approach to the treatment of hypertension should be as follows: (1) In the patient with mild and labile hypertensive disease, Rauwiloid alone is the therapy of choice. If the patient is unresponsive to this drug alone (after 6 to 8 weeks) then perhaps a combination with Apresoline or Veriloid is the therapy of choice. (2) It appears that in the case of severe but not rapidly progressing hypertensive disease, the patient should be initially treated with Rauwiloid alone. If the response is not adequate at the end of six to eight weeks, hexamethonium may then be added to a better stabilized individual who will have fewer and less severe side effects than when hexamethonium is used alone. The dose of hexamethonium must be arrived at by a titration procedure in which the amount of drug being administered is progressively increased until the desired results are obtained. (3) In the severe and rapidly progressing type (but not an acute emergency) of hypertensive disease (without renal failure), therapy must be initiated with more potent hypotensive drugs such as hexamethonium, and such stabilizing and secondary agents as Rauwiloid must be added later or used concurrently. (4) In the severe malignant type of hypertension and in cases of hypertensive emergencies, initial therapy with oral drugs is usually unsatisfactory. In these instances the administration of parenteral drugs under hospital conditions is indicated. For this purpose parenteral hexamethonium (intramuscular) or Veriloid (continuous intravenous infusion, and intramuscular) are the agents of choice. When the hypertension is well-regulated, long-term therapy can then be substituted for the emergency therapeutic approaches. Only long-term observation will furnish us information as to the rewards for such an approach to hypertension and of the eventual but as yet unseen complications of any drug therapy.

TABLE V. SUMMARY OF RECOMMENDED THERAPEUTIC APPROACH TO TREATMENT OF HYPERTENSION BASED ON SEVERITY OF DISEASE BEING TREATED

	DEGREE OF HYPERTENSION	SYMPTOMS	INITIAL TREATMENT	SUPPLEMENTARY TREATMENT IF INITIAL TREATMENT IS INADEQUATE
1.	Mild, labile	Minimal	Rauwiloid	Apresoline or Veriloid
2.	Relatively severe but unprogressive	Minimal to significant	Rauwiloid	Hexamethonium (oral or parenteral)
3.	Severe, progressive	Significant	Hexamethonium-Rauwiloid (concurrently)	Apresoline
4.	Hypertensive emergency	Severe	Parenteral hexamethonium or I.M. Veriloid	Continuous infusion of Veriloid (intravenously)*

*We have rarely observed a patient (in over 100 trials) who was unresponsive to this drug regardless of the severity of the disease.

SUMMARY

Twenty-five patients with essential hypertension have been subjected to combined Rauwiloid-hexamethonium therapy. This therapy resulted in a greater number of patients obtaining an adequate reduction of blood pressure than that from any single drug or combination of drugs previously reported from this investigative center. There was also a reduction in the frequency and severity of the unpleasant side reactions which have previously been observed when hexamethonium is used alone but the beneficial side effects of Rauwiloid have persisted. The dose of hexamethonium could be reduced on combined Rauwiloid-hexamethonium therapy, and the blood pressure was reduced further and was better stabilized. Thus, it is suggested that most patients with severe essential hypertension can be initially treated with Rauwiloid but those patients who do not respond within six to eight weeks should also be treated with hexamethonium.

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ECHINOCOCCOSIS OF THE HEART

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ECHINOCOCCAL disease occurs most commonly in sheep-raising countries.[21] Several reports have been published about the incidence of this disease in the Near East, both in human beings and in animals.[16,22-25]

The purpose of this paper is to discuss briefly echinococcal disease of the heart. Most of the literature on the subject of echinococcal disease of the heart is in Spanish and Portuguese. Only a few reports have appeared in the American and North European Medical journals.

HISTORY

There were several reports of the post-mortem findings of hydatid cysts in the heart during the nineteenth century. Griesinger in 1846 collected fifteen cases; Budd in 1858 reported five; and Neisser in 1877 reported twenty-nine additional ones. In 1905, Grulee[14] reviewed the literature and reported fifty-five cases of cardiac echinococcosis. Dévé, however, contributed most to the knowledge of this disease. In 1916, he collected reports of 105 cases,[7-9] and in 1928 the number increased to 137.[11] Up to 1945, 159 reports of echinococcosis of the heart had appeared, but only four from American sources.[1,4,14,19] In 1945, Zizmor and Szucs[26] reported one case, and Peter and his associates[20] reported eight additional ones. The last one we know of was reported by D'Abreu in 1950.[3]

PATHOGENESIS

The disease is caused by the dog tapeworm *Echinococcus granulosus*. The dog is the definitive host and is infected by eating live cysts in the viscera of sheep, cows, and camels. A recent survey showed that about 25 per cent of the stray street dogs in the principal cities of the Near East were infected with *Echinococcus granulosus*.[21]

Dévé,[10] Dew,[13] and Magath[18] suggested that the human infection takes place in childhood and that the clinical manifestations appear later in life when the slow-growing cyst enlarges sufficiently to produce symptoms.

The disease is transmitted to man by the ingestion of the eggs of *Echinococcus granulosus* from dog feces which then hatch in the duodenum. The oncospheres

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after traversing the intestinal wall enter the capillaries of the portal system and are carried to the liver. There the majority are retained, and the rest reach the lungs. The larvae that by-pass the hepatic and pulmonary filters reach the heart where some travel by way of the coronaries, lodge, and grow in the heart itself. The rest are distributed elsewhere by the systemic circulation. The incidence of involvement of the different organs by primary cysts was stated by Dévé to be as follows: 75 per cent in the liver, 8.5 per cent in the lungs, 0.5 per cent in the heart, 5.5 per cent in muscles, 2.5 per cent in spleen, 2.0 per cent in kidneys, 1.5 per cent in brain, 1.0 per cent in bone, and the rest in miscellaneous organs.

The possibility of a secondary cyst in the heart arising from a primary cyst in the lung seems unlikely since the lung filter, though permeable to the hexacanth embryo of 36 microns diameter, will not permit a scolex which is 5 or 6 times larger to pass.

The incidence of cysts in the right side of the heart is said to be more than in the left side,[14] in the proportion of about 3:2, presumably because the entrance into the right coronary artery is more direct than into the left artery.[20] Dévé, however, found that in 80 per cent of his cases, the left side of the heart was involved. He stresses the fact that the hydatid embryo reaches the heart only through the coronary arteries and that it never penetrates the endocardium.[12,15]

The cysts in the heart vary in size from that of a pea to that of the "head of a fetus,"[12] with an average diameter of 3 to 5 cm.[14] The cyst usually is single, but multiple and multilocular ones occur.[9] Dévé explains these as being secondary to the rupture of a primary intracardiac cyst.[9] The hydatid elements are then implanted either in the wall of the primary cyst or subendocardially in the neighborhood.

Cysts may be found imbedded in the myocardium, pedunculated or free in the chambers of the heart, or in the pericardium. In any of these sites, the cyst may be either living or dead. The living cyst may remain intact or rupture repeatedly. The dead cyst may become fibrosed or calcified.

Cysts within the myocardium may burst into the pericardial sac or into the heart chambers. Rupture into the pericardial sac happens in about 10 per cent of the cases of cardiac echinococcosis.[7] It usually occurs only once since the resulting pericarditis and subsequent fibrotic adhesions prevent further tears. Rupture into the heart chambers, however, is usually multiple since no adhesions develop on the endocardial surface.[12]

SYMPTOMATOLOGY

According to the clinical manifestations of cardiac echinococcosis, cases may be divided into two main groups, A and B, depending on whether they are accompanied by symptoms or not (see Table I). Symptoms may arise from the pressure of the cysts, from allergic reactions to the hydatid fluid, or from embolic phenomena. When primary intraluminal rupture occurs only microscopic embolic elements enter the systemic circulation and cause minor symptoms. After subsequent ruptures, larger particles are dislodged which may cause immediate mechanical trouble[12] as listed in Table I.

TABLE I. CLINICAL CLASSIFICATION OF ECHINOCOCCOSIS OF THE HEART

Group A. Cyst or Cysts accidentally found at necropsy

Group B. Cyst or Cysts accompanied by manifestations

- I. Pressure manifestations
  - A. On the myocardium, resulting in
    - 1. Myocardial destruction and fibrosis
    - 2. Interference with valvular action
    - 3. Interference with conduction
  - B. On the coronary sinus and coronary arteries, resulting in
    - 1. Myocardial ischemia
  - C. On the big vessels at the base of the heart
- II. Acute allergic reactions
- III. Embolic phenomena, following cyst rupture:
  - A. Intrapericardial rupture, producing
    - 1. Pericarditis and adhesions
    - 2. Pericardial cysts
  - B. Intraluminal rupture, producing
    - 1. Embolic obstruction by daughter cysts or parts of the wall of the cyst, of usually the larger arteries (femoral, renal, carotid, and pulmonary)
    - 2. Secondary cysts

DIAGNOSIS

Echinococcus disease of the heart does not give any characteristic signs by which it can be recognized. Occasional cases have been diagnosed roentgenographically[20,26] from the appearance of a rounded mass with a calcified rim in the region of the heart.[1,14] If echinococcus disease is present elsewhere in the body, coincident unexplained heart disease should lead to suspicion of cardiac echinococcosis.[14]

Electrocardiograms in patients with cardiac echinococcosis showed either nonspecific myocardial changes,[1,20,26] or conduction defects.[26] Eosinophilia, positive skin reactions to specific antigen, positive precipitation tests and complement fixation tests were reported in a variable number of cases,[1,26] but at most they are group-specific and not species-specific.[26]

PROGNOSIS

In general, the prognosis is unfavorable,[20] but patients may reach advanced age without inconvenience.[14] The disease may progress and end in one of two ways, either death without rupture of the cyst or death with rupture of the cyst[12] (see Table II).

TREATMENT

About 25 per cent or more of the patients are asymptomatic[20] and thus may not need any treatment as the cysts may regress and the larvae die.[19,26] However, if a living intact cyst in the heart causes clinical manifestations, or if the pericardium is involved either by adhesions or by cysts, then surgical treatment is

TABLE II. PROGRESS OF ECHINOCOCCOSIS OF THE HEART

Death without rupture of the cyst	
	Death due to another unrelated disease
	Sudden shock
	(? Microscopic fissure in the cyst)
	Major arrhythmia
Death with rupture of the cyst	
	Into the pericardium
	Into the heart cavities

indicated.[20] The first successful operation for echinococcal cyst of the heart was reported by Long[17] in 1932. Since then only a few surgical attempts at excision have been made, the last of which was by D'Abreu[3] in 1950.

INCIDENCE

Of the 71,388 admissions to all the services of the Hospital of the American University of Beirut during the period 1935 to 1953, 257 patients were admitted for complaints referrable to hydatid cysts. Thus the over-all incidence of hydatid disease among causes of hospital admissions is 0.36 per cent.

Of these cases 133 were hydatid disease of the liver (51.7 per cent), seventy-seven cases of the lung (29.9 per cent), fifteen cases of the kidneys (5.8 per cent), twelve cases of the spleen (4.67 per cent), nine cases in the soft tissues (3.5 per cent), seven cases in the peritoneum (2.7 per cent) and four cases in miscellaneous sites in the body: spinal cord, biliary tree, thyroid gland, and orbit. Echinococcosis of the heart was not suspected in any patient, thus its incidence cannot be computed from this series.

During the same period among 720 necropsies, hydatid cysts were found in six. In two of these cases the liver was involved alone with a single cyst. In another case a cyst in the liver and another in the gastrosplenic ligament were present. In the remaining three cases a cyst was found in the diaphragm, transverse mesocolon, and the heart, respectively.

REPORT OF CASE

K.E.H.—A white woman, aged 55 years, was admitted to the hospital in June, 1952, because of recurrent hemoptysis of one week's duration. Her past and family histories were irrelevant. For a year the patient had had episodes of stabbing precordial pain, lasting for a few minutes. Pain was accompanied by numbness in the left shoulder. The episodes were precipitated by emotional upsets and subsided on rest.

Her temperature was 39°C., pulse rate 120 per minute, respiration rate 24 per minute, and blood pressure 120/90 mm. Hg. She was pale, dyspneic, orthopneic, and had a productive cough. Her sputum was tinged with fresh blood. The cervical veins were congested and pulsating, and there was 2-plus pitting edema of her legs. There was dullness over the lower half of the right lung with inspiratory râles and decreased breath sounds and tactile fremitus. There were few inspiratory râles in the left base. The heart was not enlarged, and the sounds were regular and rhythmic. The liver was enlarged to 7 cm. below the costal margin, soft and tender. The venous pressure was 180 mm. of water. An electrocardiogram showed left ventricular enlargement and myocardial change. The leukocyte count was 15,000 per c.mm. with a differential count of 84 per cent neutrophils, 14 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils.

The erythrocyte sedimentation rate was 23 mm. in the first hour. The blood cholesterol was 315 mg. per cent and the proteins 5.96 Gm. per cent with 2.74 Gm. albumin and 3.22 Gm. globulin. The urea nitrogen was 25 mg. per cent. The CO_2 combining power was 46.7 volume per cent. Urinalysis revealed 2-plus reducing substances, finely granular casts, and 4 to 6 leukocytes per high-power field. The stools had *Taenia* ova and ova of *Trichuris trichuria*. The sputum contained no acid-fast bacilli.

The patient received digitoxin 0.6 mg. the first two days and then 0.2 mg. daily. Dicumarol in 200 and 100 mg. doses was given on the first two days of hospitalization. A roentgenogram of the chest showed a bulge in the cardiac shadow in the left lower contour.

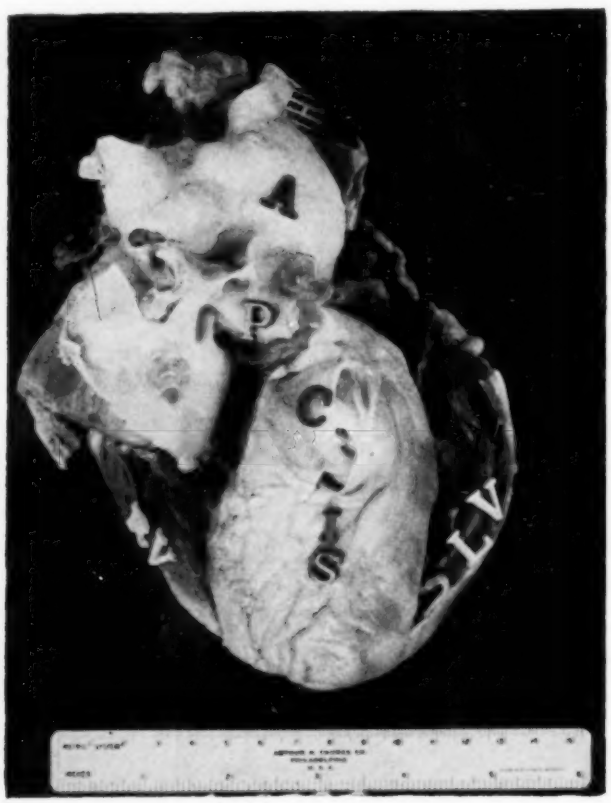

Fig. 1.—Hydatid cyst of the heart. The cyst (c) is incised, and the chitinous membrane reflected at the upper right part. *A*, Aorta; *P*, Pulmonary artery; *LV*, Left ventricle; *IS*, Interventricular septum; *C*, Cyst.

The condition of the patient remained rather static, but seven days later there was sudden substernal pain and hemoptysis and she collapsed. Oxygen inhalation, artificial respiration, and cardiac stimulants were of no avail, and the patient died.

Post-Mortem Examination.—

Thoracic cavity: There were 450 and 50 c.c. of serosanguineous fluid in the right and left pleural cavities, respectively. The right lung weighed 550 grams and the left 650 grams. The lower parts of the middle and lower right lobes, the anteroinferior part of the upper left lobe, and the anterosuperior part of the lower left lobe showed slightly elevated firm areas of hardened

reddish brown tissue. Microscopic study of these areas showed them to be red infarcts surrounded by congestion. The pericardial surfaces were smooth and glistening. Overlying the superior part of the interventricular septum on the anterior surface of the heart there was a cystic mass 4 cm. in diameter (Fig. 1). Grossly, the cyst was lined by a chitinous membrane and contained clear fluid in which scolices and hooklets were found. The anterior descending branch of the left coronary artery coursed beneath the cyst. Its upper part was calcified and greatly narrowed below the cyst. The myocardium of the left ventricle showed areas of scarring to which thrombi were attached.

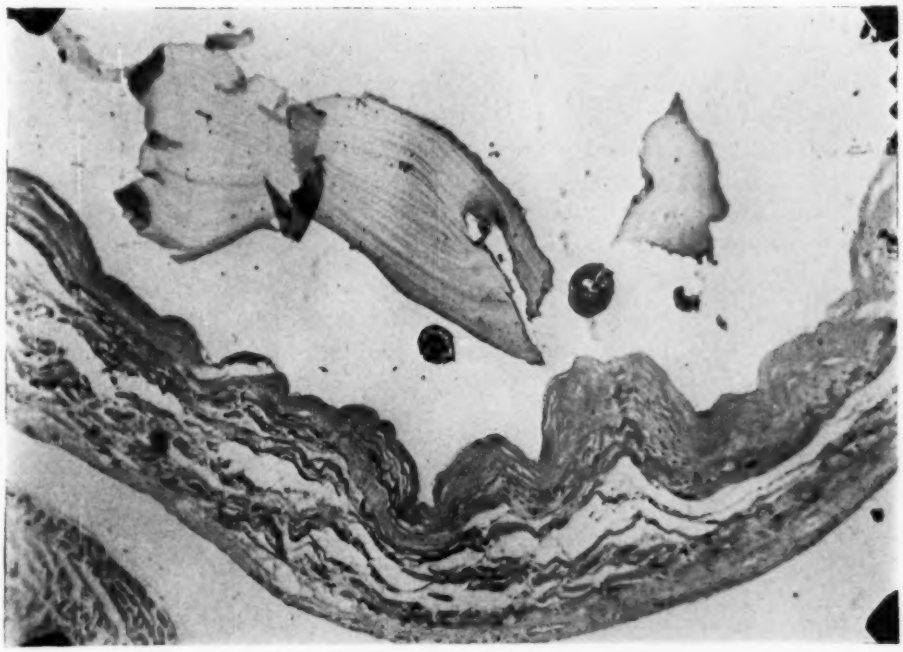

Fig. 2.—Hydatid cyst of the heart: Microscopic picture of cyst shown in Fig. 1. The lamellated, acellular chitinous membrane is seen attached to the fibrous coat of the cyst wall. Two scolices are seen in the center. The right scolex shows hooklets. The myocardial bundles seen in the lower field are atrophic. Hematoxylin-eosin stain × 70.

Microscopic examination: The cyst rested between the visceral pericardium and the myocardium (Fig. 2). The anterior descending branch of the left coronary artery was calcified. There was a granulating hemorrhagic area adjacent to an atheromatous patch, and the lower lumen contained fresh thrombi. In the left ventricle, the anterolateral wall showed areas of acute necrosis of the myocardium with mild leukocytic infiltration together with areas of fibrous scar tissue on the endocardial aspect to which thrombi were attached. The right ventricle showed small foci of fibrosis in the myocardium. Microscopic study of the conduction system did not show any special lesions.

Examination of the abdominal contents revealed passive congestion of the liver, spleen, and kidneys. No other hydatid cysts were found in the body (the skull was not opened).

COMMENT

In this case of echinococcal disease of the heart, some of the adverse anatomic and physiologic effects of the cyst were shown. It was at least in part responsible for the fibrosis and narrowing of that portion of the anterior descending branch of the left coronary artery on which it rested. It was evident that the cyst caused

pressure and narrowing of the lumen and further helped to decrease the circulation of that portion of the myocardium supplied by this important branch of the coronary system. The combination of circumstances, no doubt, played an important role in the resultant thrombosis of the terminal part of this artery.

On physiologic grounds it was considered that the above findings partially explained the progressive deterioration of the condition of this patient in spite of all the medical care given and may partially explain the repeated fresh infarction of the lungs in spite of the use of anticoagulant therapy and the reduction of the prothrombin time to the dangerous level of 60 minutes (control 15 minutes).

Now that cardiac surgery in general is on a firm basis the excision of echinococcal cysts of the heart promises success, provided early diagnosis is made. Early diagnosis, however, is not easy. Among fifty-six cases studied post mortem, only in six cases was the diagnosis made prior to death.[20] The most important diagnostic aid is roentgenography, and any abnormal shadow on the contour of the heart should be suspected and careful study made for echinococcal disease.

SUMMARY

In reviewing the literature 169 cases of echinococcosis of the heart were mentioned.

In a series of 257 patients with hydatid disease admitted to the American University Hospital of Beirut, Lebanon, the liver was involved in 51.7 per cent, the lung in 29.9 per cent, the kidneys in 5.8 per cent, the spleen in 4.67 per cent, the soft tissues in 3.5 per cent, and the peritoneum in 2.7 per cent of the cases. One cyst was also found in each of these, the spinal cord, biliary tree, and orbit. The thyroid in one case had two cysts.

In a series of 720 necropsies, hydatid cysts were found in six. Of these one cyst was found in the heart.

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Clinical Reports

RHEUMATIC HEART DISEASE IN DEXTROCARDIA WITH COMPLETE SITUS INVERSUS

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RHEUMATIC heart disease in dextrocardia is a rare condition, particularly if associated with complete situs inversus, the so-called mirror type dextrocardia. Only five such cases were reported in the literature. The purpose of this paper is to review these cases and to add one of our observations.

In 1933, Pavel[1] described a case of postrheumatic aortic insufficiency. In 1942, Pasternack[2] and Abbott and Russek[3] reported one of calcareous aortic stenosis of rheumatic origin. Mitral insufficiency and stenosis associated with rheumatic fever were observed by Silberstein and Steinberg[4] in 1943 and by Panek[5] in 1948. Three years earlier, Parson[6] recorded a case of rheumatic heart disease with aortic and mitral valve involvement. In all these cases, the rheumatic changes took place in a right-sided heart with total transposition of the viscera (Table I). The very first case of mitral stenosis in a mirror type dextrocardia was

TABLE I. REPORTED CASES OF RHEUMATIC HEART DISEASES IN DEXTROCARDIA WITH COMPLETE SITUS INVERSUS

AUTHOR	YEAR	AGE AND SEX	RACE	AGE AT FIRST RHEUMATIC ATTACK (YEARS)	TYPE OF VALVE INVOLVEMENT	AGE AT DEATH (YEARS)
Pavel	1933	29 M	White	7	Aortic insufficiency	Not stated
Abbott and Russek Pasternack	1942	43 M	White	?	Aortic stenosis	43
Silberstein and Steinberg	1943	33 F	White	13	Mitral insufficiency and stenosis	Not stated
Parson	1945	24 F	White	21	Combined aortic and mitral lesion	24
Panek	1948	45 F	White	9	Mitral insufficiency and stenosis	Not stated
Bleyer and Saphir	1953	36 F	Negro	18	Mitral insufficiency and stenosis	Still living

From the Medical Department of the Cook County Hospital, Chicago, Ill.
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reported by Owen[7] who stated, however, that he could find no etiologic factor for the mitral stenosis.

CASE REPORT

D.V., a 36-year-old Negro woman, was admitted to the Medical Ward of Cook County Hospital (service of Dr. H. J. Isaacs) on Aug. 20, 1952. The chief complaints were unproductive cough and shortness of breath on exertion for several days. Past history revealed that dextrocardia and situs inversus were first diagnosed in a hospital in 1934, where she was treated for an initial attack of migratory arthritis and heart failure. At that time, the blood serology showed 3+ Kahn and 4+ Kline. Two years later she had a miscarriage. The next bout of rheumatic fever occurred in 1945. Thereafter, she felt perfectly well and was able to work as a housekeeper. She was first admitted to this hospital in March, 1950, for the treatment of a left lower lobe pneumonia. At that time, dextrocardia and complete situs inversus were again noticed. The point of maximum impulse was felt in the sixth intercostalspace, at the right anterior axillary line. A harsh systolic murmur was heard at the apex. The electrocardiogram showed sinus rhythm and the typical signs of dextrocardia: inversion of all waves in Lead I and the interchange of Leads II and III (Fig. 1). The blood Kahn and Wassermann reactions were again positive. The patient made an uneventful recovery and was discharged.

She remained well until early 1952 when she gradually became short of breath on exertion and had pain in the right knee. Subsequently, moderate heart failure necessitated hospitalization on two occasions. On the second admission, a Grade 3 systolic murmur was heard all over the precordium and a soft diastolic murmur over the apex. For the first time, auricular fibrillation was observed which persisted at the time of her third admission.

Her father died at 56 years of age of "heart dropsy", her mother at 61 years of a "heart attack." This was the cause of death also in one of her sisters, who died at the age of 31, while another sister died at 33 years of age of a "stroke." The patient does not know whether any of her brothers or sisters had dextrocardia. She writes with the right hand but does most of her work with the left hand.

Physical examination, on admission, revealed a well-developed and moderately nourished Negro woman, alert and cooperative. Her temperature was 98.4°F. (36.8°C.) rectally; the pulse rate was 84, irregular in time and force; the respiratory rate was 20 per minute, the blood pressure 100 mm. Hg systolic and 70 mm. diastolic. Her height was 63 inches, her weight 128 pounds.

The pupils were round, equal, and reacted normally to light and accommodation. There was no cyanosis. The throat was moderately injected. The breasts were normal. There was a slight bulging of the right chest anteriorly. The lungs were resonant, the breath sounds normal. There were dry inspiratory râles and wheezing all over the chest. The point of maximum impulse of the heart was in the right anterior axillary line, in the sixth intercostal space. At this point, the first heart sound was accentuated and a harsh, Grade 3 systolic and a Grade 2 mid-diastolic murmurs were heard. No murmurs were noticed over the remaining precordium. The rhythm was grossly irregular, the rate 84 beats per minute. No pulse deficit was present. The femoral pulse was palpable and equal on both sides. The liver edge was felt on the left side, three finger breadths below the left costal margin in the mid-clavicular line. It was soft and tender. The spleen was not felt. There was no clubbing of the fingers or toes. One plus dependent edema was noticed.

The laboratory findings were as follows: the red blood count was 4,170,000, the hemoglobin, 81 per cent. The platelet count was normal. The white blood count was 8,900 with 56 per cent neutrophiles, 7 per cent bands, 5 per cent eosinophiles, 26 per cent lymphocytes, and 6 per cent monocytes. The urinalysis was normal. The fasting blood sugar was 106 mg. per cent. The blood Kahn and Wassermann reactions were positive. The Kahn titer was 56 units. The vital capacity was 1,100 c.c. (normal value for patient's height and weight 2,900 c.c.). The circulation time was: arm-to-lung (ether), 8 seconds and arm-to-tongue (decholin), 21 seconds. The electrocardiogram was done three days after admission. Leads I, II, III, aV_R, and aV_F were taken in the usual manner while the V leads were taken across the right chest in the same

way as they are taken across the left chest, when the heart is in normal position (Fig. 2). They revealed auricular fibrillation with approximate auricular rate of 375 and a ventricular rate of 100. The f waves appeared as fine, irregular undulations in all leads except in V_1 and V_2, where they occurred as coarse, biphasic waves. Duration of QRS was 0.08 second. There was a tall R in Leads II, III, aV_F, $V_{5,6}$. The T was negative in Leads I, II, III and aV_F; aV_R showed an RS pattern, while aV_F was of a QR pattern. The transition zone was between V_4 and V_5.

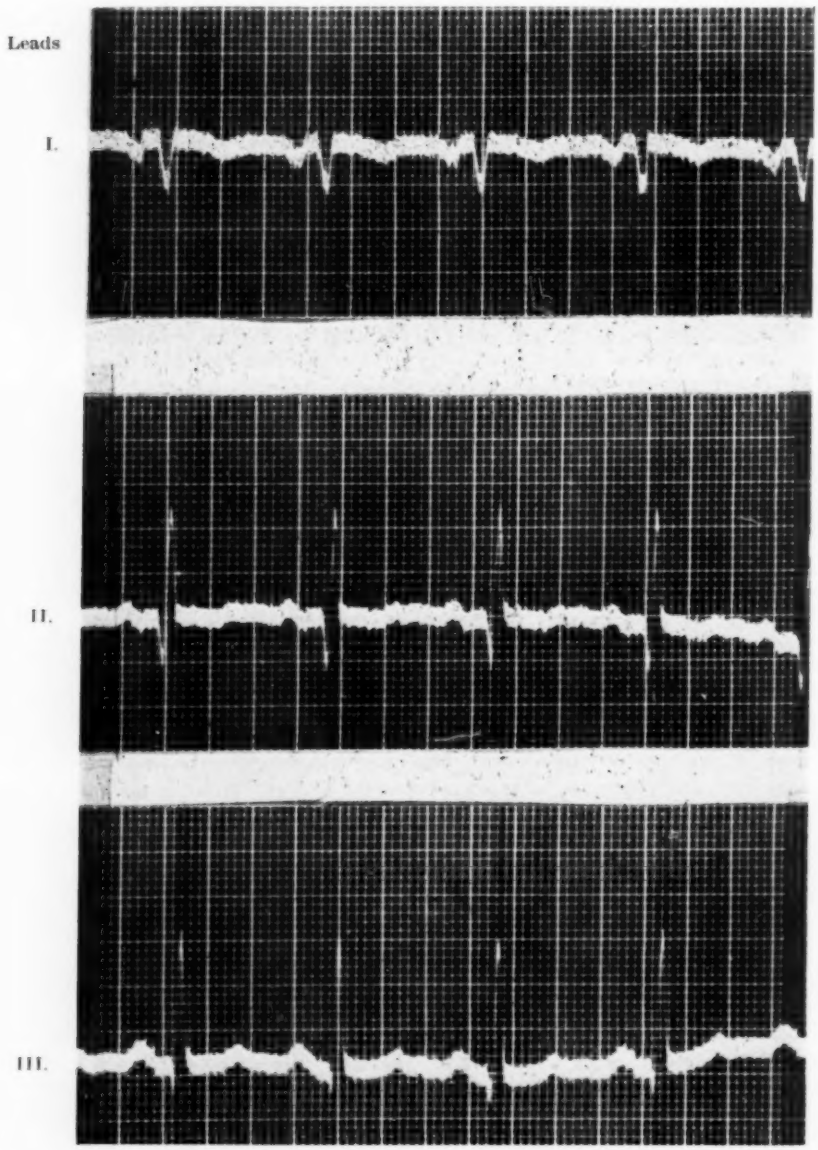

Fig. 1.—Electrocardiogram taken in March, 1950, showing inversion of all waves in Lead I, and interchanging of Leads II and III.

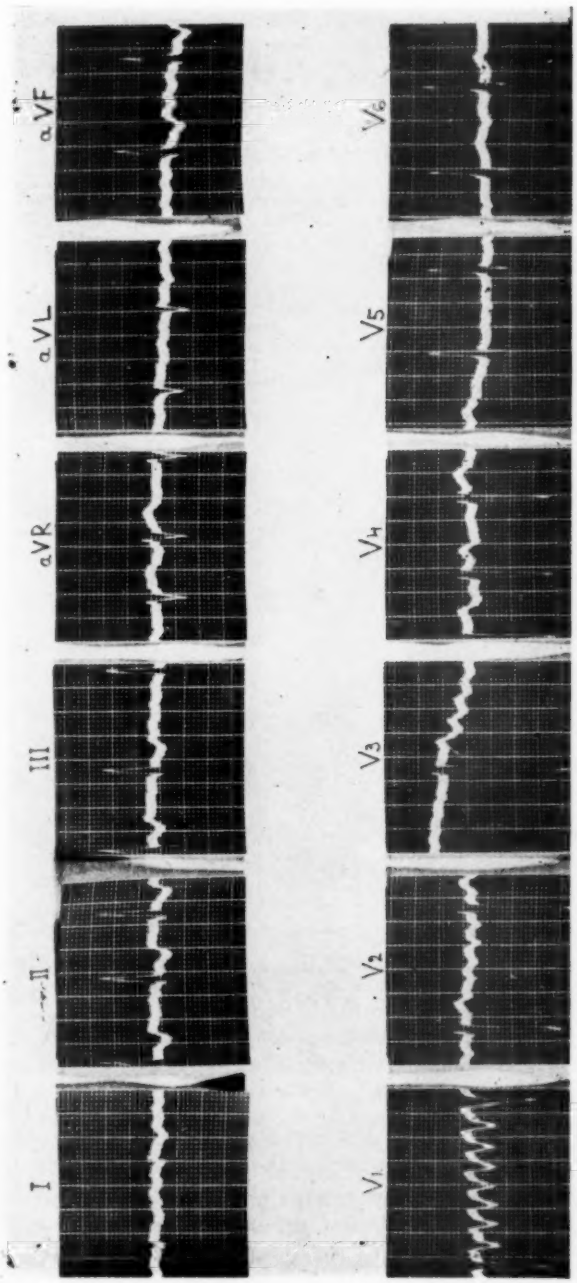

Fig. 2.—Electrocardiogram taken in August, 1952, showing auricular fibrillation and characteristics of dextrocardia.

Teleroentgenogram (Fig. 3) showed the heart grossly enlarged to the right and left. The maximum heart measurement to the right was 12.7 cm. and to the left 5.6 cm. There was a marked prominence of the pulmonary segment while the aortic knob appeared small and hypoplastic. The lung fields revealed some passive congestion. The stomach air bubble was well visualized under the right leaf of the diphragm. Fluroscopy revealed the point of opposite pulsation displaced downward. In the left anterior oblique position, the retrosternal space appeared narrow due to bulging of the right ventricle. The esophagus was displaced posteriorly suggesting left auricular enlargement. The roentgenogram of the paranasal sinuses was within normal limits. Barium studies indicated a transposition of the colon.

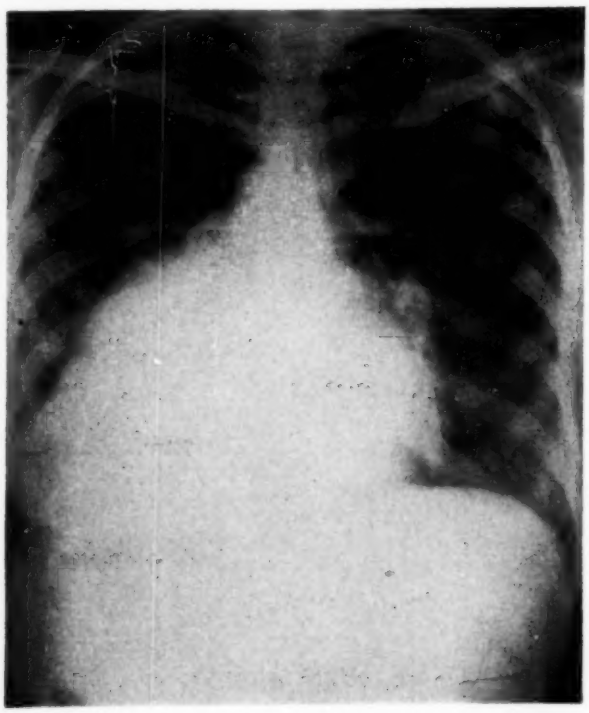

Fig. 3.—Teleroentgenogram showing cardiomegaly and dextrocardia.

An angiocardiogram was done by courtesy of the Cardio-Physiologic Department, Cook County Children's Hospital, under the direction of Benjamin M. Gasul, M.D. Dr. Gasul's report follows: . . . "50 c.c. of 75 per cent Neo-Iopax were injected into the left cubical vein. The vena cava superior was visualized on the left side. The dye entered from the superior vena cava into the right auricle, which was situated on the left side of the heart, and then into the right ventricle which occupied the left and the midanterior portion of the cardiac silhouette. The main pulmonary artery was seen two seconds after the injection of the dye on the right cardiac border. The subsequent plates, all taken in one-half second intervals, show a large right and left pulmonary artery coming off the main pulmonary artery. The left ventricle and the aorta were not visualized at the end of 13 seconds, evidently because of the prolonged circulation time.

The information obtained from the angiocardiography reveals that the superior vena cava is on the left side, as well as the right auricle and the right ventricle, while the pulmonary artery is located on the right side which means that there is dextrocardia."

Course: Treatment consists in bed rest, digitalization, ammonium chloride, mercurials, and low salt diet. The cough and pulmonary congestion subsided, the peripheral edema disappeared and the liver congestion receded. As soon as compensation was established, patient was put on

antiluetic therapy. She received six million units of long-acting procaine penicillin over a period of ten days without any apparent side effects on any part of the cardiovascular or other systems. On Oct. 18, 1952, the patient was discharged free from complaints and referred to the Cardiac Clinic of this hospital for follow-up.

COMMENT

The diagnosis of dextrocardia with complete situs inversus, rheumatic mitral insufficiency and stenosis appeared well established by the history of recurrent attacks of polyarthritis and heart failure, the physical findings, the characteristic roentgenogram of the chest, and the barium studies of the intestines, as well as by the angiocardiogram and the electrocardiogram. Although the serologic tests for syphilis were positive, clinical signs suggestive of cardiovascular syphilis were absent.

The electrocardiogram, taken on the patient's first admission and shown in Fig. 1, is pathognomonic of dextrocardia with complete situs inversus. It is characterized by the inversion of all waves in Lead I and the interchange of Leads II and III. At the time when the patient was fibrillating, the absence of P waves would have made it impossible to demonstrate dextrocardia by the standard limb leads only. Lead aV_R, facing the left ventricle, should show a QR pattern as it does in uncomplicated dextrocardias (Goldberger[8]). In our case, however, we find an RS pattern which is probably due to vertical heart position. The reason for the QR pattern instead of a RSR^1 one in aV_F is a probable forward rotation of the apex. Furthermore, there is also a clockwise rotation of the heart.

Auricular fibrillation in mirror type dextrocardia with rheumatic changes has not been, to our knowledge, described so far. However, auricular fibrillation in congenital dextrocardia was observed and reported twice before; first, by Krestin[9] in 1927, and later by Lloyd[10] in 1934. Krestin's case was a 30-year-old woman who had a dextrocardia with mitral stenosis of rheumatic origin but without total situs inversus. In Lloyd's report auricular fibrillation, explained by diphtheria, was found in a 63-year-old man, who had a mirror type dextrocardia but had no history or other findings suggestive of rheumatic heart disease.

Analysis of the reported cases and of our own of dextrocardia with rheumatic valvular disease in complete situs inversus shows that this condition was found, so far, only in white persons, our patient being the first Negro one. The pure mitral lesions, as well as the one case of combined mitral and aortic changes, were encountered in women while the two aortic cases were found in men. This corresponds with the well-known fact that rheumatic aortic lesions are more common in men while rheumatic mitral changes occur predominantly in women. The diagnosis of dextrocardia and rheumatic involvement was made clinically in the case of Pasternack and Abbott and Russek and confirmed by autopsy. In all other cases, the diagnosis was established clinically, from the history, physical examination, roentgenographic studies of the chest and bowels, and electrocardiographic findings. Furthermore, contrast cardiovascular visualization was employed as a diagnostic aid in the case of Silberstein and Steinberg, as well as in our own.

The age of onset, the duration, and the course of the rheumatic disease, in all reviewed cases, showed the same pattern which is generally found in rheumatic heart disease without dextrocardia. This fact tends to confirm the opinion of Friedberg,[11] Holzmann,[12] Levine,[13] Taussig,[14] White,[15] that dextrocardia by itself, associated with complete situs inversus, is a benign condition which does not affect activity or duration of life. Only Panek[5] believes that dextrocardia by itself, with or without situs inversus, predisposes to different ailments of the heart. There was no indication in our case that dextrocardia per se influenced unfavorably the disease process or the response to treatment.

SUMMARY

1. The literature on rheumatic heart disease in dextrocardia with complete situs inversus is reviewed.

2. An additional case, the first observed in a Negro patient, is herewith reported.

3. Rheumatic heart disease in mirror type dextrocardia appears to follow a similar course as seen in normally situated hearts.

Our thanks are due to Vlastimil Vrla, M.D., who kindly translated the original Czech articles mentioned in this paper.

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FUNCTIONAL COR TRILOCULARE

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THE congenital anomalies associated with dextrocardia are many and often bizarre. We have recently observed such a situation terminating in death at age 47.

The patient had been cyanotic since birth with noticeable clubbing of his fingers and toes since childhood. His activities had always been limited by dyspnea on exertion, and he had often been told by physicians that his heart was in the wrong side of his chest. There were a number of episodes of edema beginning at age 12, becoming persistent at about age 40. Hemoptysis was a commonplace event after age 13. He was able to do light work during most of his life, being employed as captain of a small excursion boat for his last 15 years.

In the fall of 1949 at age 47 the patient had his first episode of paroxysmal rapid heart beat lasting several hours. These attacks occurred at widely spaced intervals but on May 19, 1950, he was admitted to the hospital with tachycardia of 3 days duration associated with palpitation, dyspnea, fatigue, and substernal pain radiating down both arms.

The patient was an acutely ill, thin white man, deeply cyanotic, gasping for breath and complaining of chest pain. (T. 98.6, P. 150, Wt. 110 pounds, B.P. 90/60 mm. Hg). Neck veins were distended. Fine râles were heard at both lung bases. The heart was found in the right chest and the point of maximal impulse in the sixth right intercostal space in the anterior axillary line. By percussion the heart was large, extending from the right midaxillary line to the left sternal border. A very loud rough systolic murmur was heard in the fourth right intercostal space at the sternal border. Softer systolic murmurs were heard at the cardiac apex and in the second right intercostal space. The liver was felt 4 cm. below the xyphoid in the epigastrium and extended into the left upper abdominal quadrant but not the right. Ankle edema was noted as well as striking clubbing of the fingers and toes.

An admission electrocardiogram was interpreted as showing paroxysmal auricular tachycardia, and quinidine was administered with reversion to an atrioventricular nodal rhythm at a rate of 60 per minute. Rest, low salt diet, mercurial diuretics, and digitalization resulted in great improvement in the patient's cardiac decompensation.

Laboratory findings included a negative serologic test for syphilis and normal urinalysis. Blood count showed normal white cells with 5,700,000 red cells and a hemoglobin of 18 Gm.

Chest roentgenograms showed bilateral apical pulmonary blebs, dextrocardia, and massive enlargement of all cardiac chambers. The aorta could not be identified with certainty but two parallel curved linear areas of calcification above the heart shadow were seen and thought to be in the pulmonary artery. On fluoroscopic examination the left branch of the pulmonary artery was enlarged and was seen to pulsate with abnormal vigor, interpreted as indicating hypertension

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in the lesser circulation. A roentgenogram of the abdomen showed a normally placed stomach. Additional electrocardiograms showed sinus or auriculoventricular nodal rhythm with varying degrees of atrioventricular block and a prolongation and abnormality of ventricular complexes interpreted as bundle branch block. Chamber inversion was thought to accompany the dextrocardia because of the transition of right ventricular pattern in V_{1R} over the left fourth intercostal space near the sternum to left ventricular pattern in V_{6R} in the right midaxillary line.

The patient was allowed to go home on July 1, 1950, but returned after one week with an attack of paroxysmal tachycardia accompanied by anginal pain, apparently precipitated by an emotional upset. The tachycardia ended spontaneously within an hour, and complete heart block appeared with nodal rhythm and multiple ventricular premature systoles. On July 14, 1950 an attack of syncope with a pulse rate of 40 occurred. Subsequent electrocardiograms showed a wandering pacemaker with incomplete heart block. The patient appeared improved the next day but died suddenly that evening.

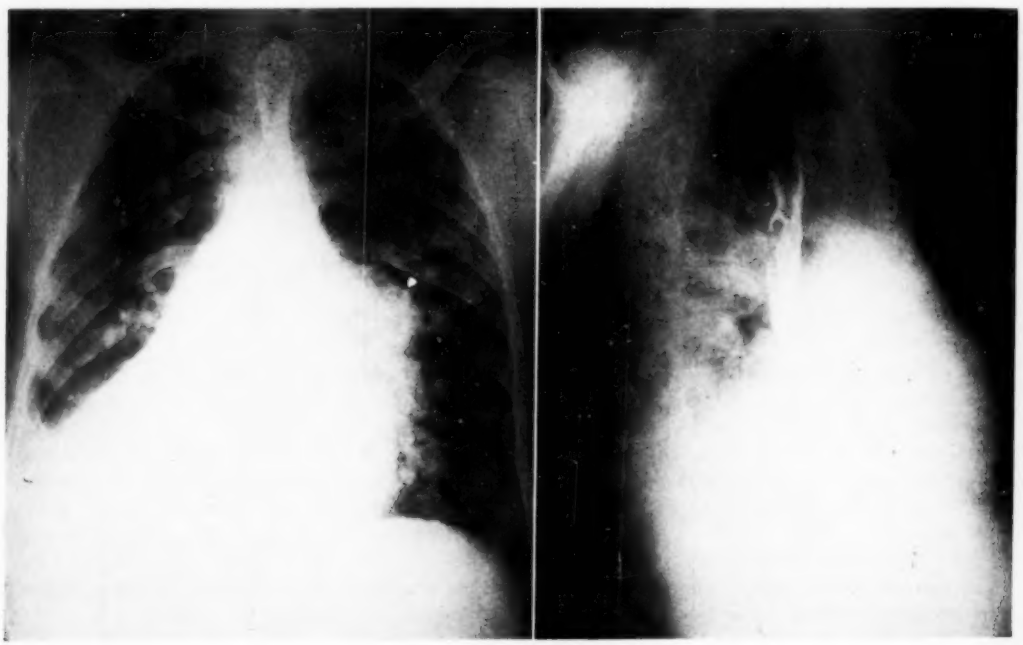

Fig. 1. Fig. 2.

Fig. 1.—Chest roentgenogram, posteroanterior. Note the absence of an aortic knob shadow.
Fig. 2.—Chest rentgenogram, right anterior oblique. Note the line of calcium above the heart.

Post-morten examination was performed by Dr. Albert L. Steplock and showed apical pulmonary blebs bilaterally and chronic pulmonary congestion. Each lung weighed 650 grams. The heart occupied a position to the right of the midline and was enlarged, weighing 600 grams. The position was somewhat vertical, one ventricle being anterior, slightly cephalad and to the left, the other posterior, slightly caudad and to the right. The vena cava emptied into a dilated atrium with walls 4 to 5 mm. in thickness. This emptied into the enlarged anterior ventricle with muscular thickness of 15 mm. This chamber, which we believe probably represented the right ventricle, gave rise to both the pulmonary artery and the aorta. The latter was small with anterior arching to the left and coursing to the left of the esophagus. It measured 5 cm. in circumference and contained no atherosclerosis. The former was posterior and to the left of the aorta. It was large, measuring 10.5 cm. in circumference and heavily calcified. All of its branches were dilated. The aortic valve was anterior and to the right in the ventricle, measuring

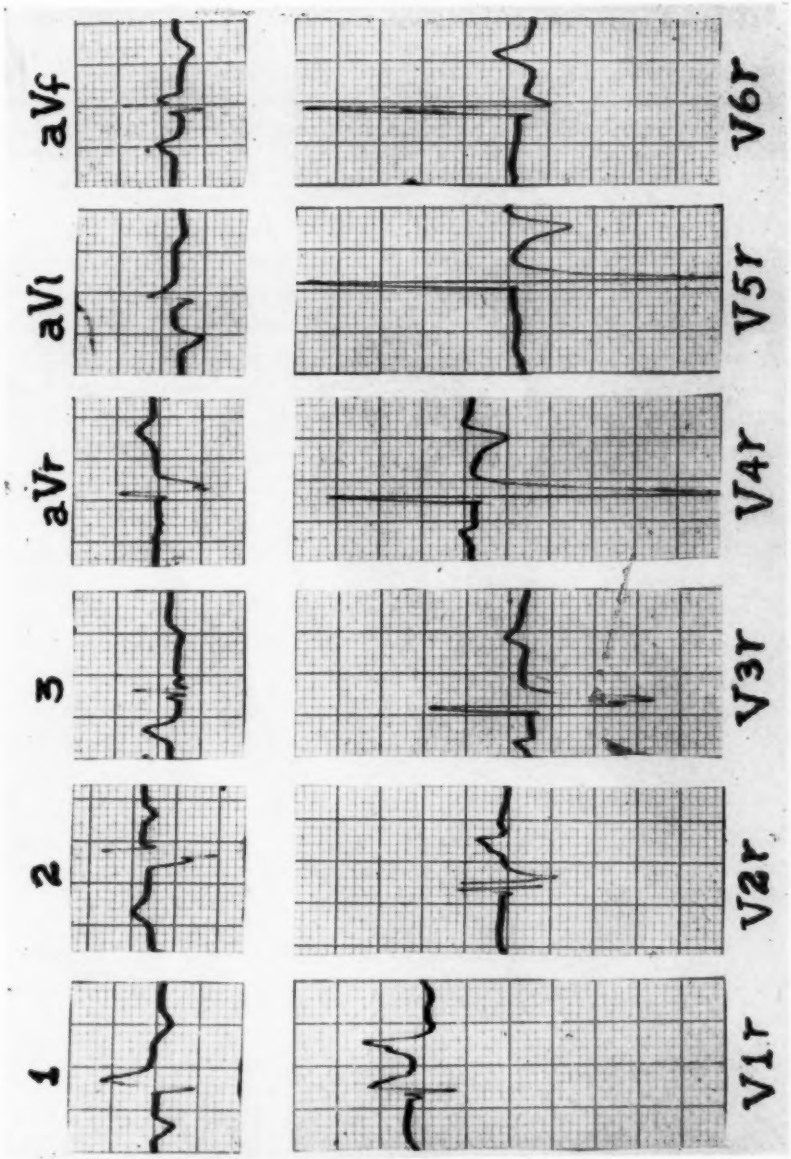

Fig. 3.—Electrocardiogram taken in June, 1950, showing sinus rhythm. The precordial leads are taken with V_{1R} in the normal V_2 position, V_{2R} in the usual V_1 position, the remainder in right chest positions corresponding to conventional left chest leads.

5.5 centimeters. The leaflets were normal. The coronary ostia were patent. Slightly posterior and to the left of the aortic ring was an irregular calcified and distorted pulmonary valve with partial fusion of one of the commissures. No vegetations were seen. The large pulmonary artery showed innumerable large slightly ulcerated calcific plagues. Four large pulmonary veins emptied into a dilated atrium 4 to 5 mm. in thickness. This chamber communicated with the posterior ventricle which we feel was the left ventricle. It was dilated, 15 mm. in thickness, and had no outlet save a large defect in the superior portion of the interventricular septum admitting three fingers.

The liver weighed 1,620 grams. The left lobe was enlarged occupying a left upper quadrant position. The ascending colon occupied a midline position posterior to the small intestine, the transverse colon having a tortuous course in the mid-epigastrium. The right gutter was empty. The left kidney was elevated with the upper pole tipped outward at a forty-five degree angle. The spleen weighed 300 grams as did each kidney.

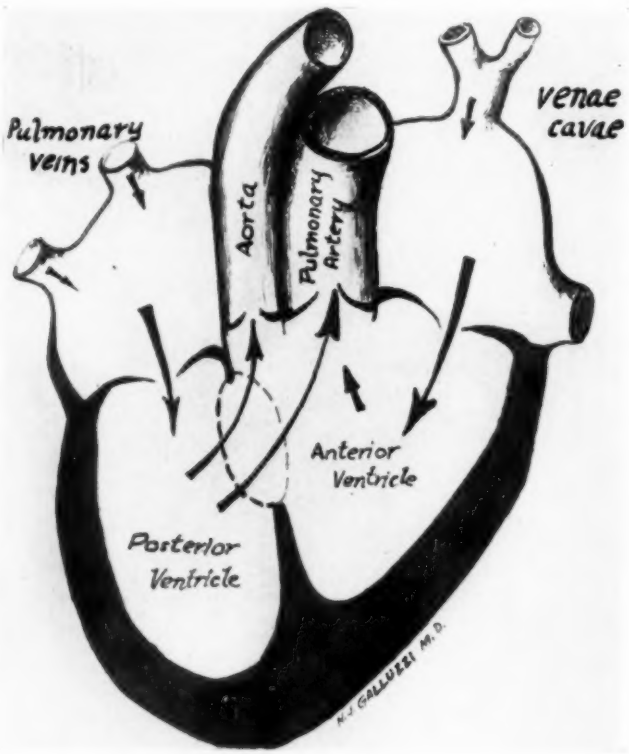

Fig. 4.—Diagram of the heart at autopsy. Probable direction of blood flow is indicated by the arrows.

Microscopic review showed a moderate degree of intimal thickening and leukocyte infiltration of the coronary arteries. The myocardial fibers were large with poor cross striation, and fragmentation was marked. There was an increase in interstitial fibrous tissue. The lungs showed small alveolae with thickened folded walls and dilated capillaries. Many heart failure cells were seen in the alveolar walls and alveolae. Blood vessels were numerous, arterioles thick-walled and tortuous with arteriosclerotic changes in the larger vessels. Chronic passive congestion was noted in all organs.

DISCUSSION

It is remarkable that a patient with such extensive congenital cardiac disease could survive to age 47. The key anomaly, aside from dextrocardia, appeared to be the origin of the pulmonary artery and aorta from the same ventricle, leaving the other without an outlet except the high interventricular septal defect. Without the latter, life would have been impossible and with it the patient had, in effect, almost a three-chambered heart. The aorta and pulmonary artery were perfused at a common pressure resulting in low systemic blood pressure and very high pulmonary pressure. Hemoptysis is understandable, and no doubt pulmonary factors were added to the almost complete arteriovenous mixing to explain the cyanosis. The loud rough systolic murmur heard in the fourth right intercostal space was probably produced by the stenotic calcified pulmonary valve although the interventricular septal defect might have played some part.

The explanation of the patient's longevity may lie in two ameliorating factors. The interventricular septum appears to have been so situated that it deflected the outflow stream of the posterior ventricle favoring entrance of oxygenated blood into the aorta. The pulmonary valvular lesion and the thickening of the pulmonary arteriolar walls both served to protect the pulmonary capillaries against excessive pressure.

It is probably unjustified to make fine interpretations of the electrocardiograms. The ventricular complexes observed are such as one might expect, assuming that the anterior ventricle was indeed the right and that a right bundle branch block was present. Since considerable hypertrophy and fibrosis of both ventricles were found, one cannot say more than that the ventricular complexes were widened and distorted by conduction delay, the anterior ventricle being the more severely affected. The inverted P wave in Lead aV_L suggests origin of the auricular impulse in the myocardium facing the left shoulder, and the presence of typical left ventricular epicardial patterns in the right axilla supports our belief that the posterior caudad ventricle was the left ventricle. The varying degrees of atrioventricular block observed were probably due to myocardial fibrosis, and a Stokes-Adams attack associated with a sudden onset of complete heart block seems to be an attractive explanation for the patient's death.

SUMMARY

We have presented the clinical and pathologic data on a patient with malrotation of the colon, dextrocardia, common ventricular origin of the aorta and pulmonary artery, and patent interventricular septum.

We feel that this represents an unusual variant of transposition of the great vessels.

Review of Meeting

REVIEW

FOURTH INTER-AMERICAN CONGRESS OF CARDIOLOGY, BUENOS AIRES, ARGENTINA, 1952

PART II

PEDRO COSSIO, M.D., AND HECTOR CAUL, M.D.

BUENOS AIRES, ARGENTINA

CLINICAL

95. An extensive paper is presented on Bernheim's syndrome or dextroventricular stenosis caused by the dilatation at the left ventricle compressing the cavity of the right ventricle through interventricular septum.

96, 97. In myxedema the considerable enlargement of the heart is very often due to pericardial effusion and disappears with proper therapy in a short period of time, 3 to 14 weeks. Occasionally there is no apparent cardiac enlargement on roentgenogram; although the size of the heart is unchanged after thyroid treatment, remarkable clinical and electrocardiographic improvement occurs. Angina pectoris was observed in only one case out of sixteen.

98. In considering the clinical course and prognosis of rheumatic fever in children, it is advisable to group them in six classes: (1) Rheumatic pains not connected with rheumatic fever, only 15 per cent of these showed rheumatic manifestations later. (2) Rheumatic fever without carditis, 75 per cent remained without heart involvement and the mortality is very low. (3) Rheumatic carditis without initial heart enlargement, 34 per cent died or remained invalids. (4) Carditis with initial heart enlargement, 60 per cent mortality or invalidism resulted. (5) Carditis with initial heart failure, 80 per cent mortality or invalidism with only a 7 per cent chance of cure. (6) Chronic rheumatic valvular disease without antecedents in which prognosis is determined by the valvular damage.

99. It was advocated that a law should be sanctioned to favor heart patients fit for work. Sedentary jobs, such as, janitors, watchmen, liftboys, and telephone operators should be reserved for such people and a certain percentage of office jobs should also be kept open. A special fund could be formed by the employees, employers, and the state, to cover indemnity.

100. In noncomplicated persistent ductus arteriosus the arterial saturation of hemoglobin is not above 95 per cent preoperatively. Two months after

surgery there was always an increase in this figure. Undoubtedly there was a short circuit from the pulmonary artery to the aorta and as the pressure in the pulmonary artery was always lower than in the aorta the possible mechanism might be the aspiration of blood into the aorta due to the great speed in this vessel.

101. Pulmonary hypertension is a frequent finding in persistent ductus arteriosus and this should be classed in three groups: (1) With pulmonary pressure ranging from 31 to 60 mm. Hg the clinical picture is like that of persistent ductus arteriosus without pulmonary hypertension. (2) When the pressure in the pulmonary arteries is between 60 and 95 mm. Hg, there is already a moderate strain on the right ventricle and increased pulmonary second sound and occasionally a diastolic rumble at the apex. There is a deep S in V_1 and V_2, a tall and delayed R, and a high pointed T in the left precordial leads and an almost mitral P. (3) When the pulmonary pressure figures are 95 to 130 mm. Hg, and occasionally higher than those in the aorta, the blood flow from the aorta to the pulmonary artery is difficult and may exist only at a certain period of the heart cycle or can be reversed. Cyanosis sets in, the murmur is fragmented, and noncontinuous, and at times disappears. There is a marked strain on the right ventricle; A_{QRS} and A_T deviate towards the right. R in V_1 and V_2 are tall and delayed. Diagnosis is difficult and occasionally catheterization of the ductus has to be performed. On the whole these cases benefit by surgery.

102. A paper based on simultaneous phonocardiograms, phleboarteriograms, and electrocardiograms detects four sounds at the level of the femoral vessels which may be isolated or combined indifferently: (1) A presystolic sound originated at the level of the femoral vein due to an increase of local venous pressure caused by right auricular systole when there is venous stasis. (2) Diastolic arterial sound, due to rapid distention of the artery. (3) Postdiastolic arterial sound, possibly originated by the backward flow in the veins producing a vibration of the venal valves. (4) Venous stasis sound corresponding to the V of the phlebogram.

103. The hyperabduction syndrome described by Wright is very often associated with a Raynaud syndrome and may initiate or aggravate the latter. When conservative treatment fails, surgery including claviculectomy, scalenotomy, and other procedures should be tried.

104. A vascular syndrome of the upper limb caused by oily injections at the level of the deltoid muscle is described. The clinical features were predominantly on the skin around the injected area and at the distal extremity of the limb. Favorable results are reported from sympathetic block.

105. Sublingual nitroglycerine proves useful as a test to discriminate functional from organic peripheral vascular disease and to establish how much vasospasm is added to organic occlusion. The readings should be made in less than three minutes.

106. A report on 100 patients with arteriosclerosis obliterans in Mexico showed the following figures: 16 per cent women, 87 per cent above 50, two diabetics below 40, eleven between 40 and 50, 83 per cent smokers. Intermittent claudication was present in 80 per cent. The other had paresthesias or ulceration.

Indians are not prone to this disease and only one in this series had it. Ninety-one per cent had pathological electrocardiograms: twenty with myocardial ischemia; nine, myocardial infarction; forty-four, diffuse lesions; fifteen cor pulmonale. Five per cent required amputation of one leg. There was only one death caused by coronary and pulmonary thrombosis.

107. Chronic occlusion by arteriosclerosis of the abdominal aorta and iliac arteries should be considered as an etiologic feature in chronic ischemia of the lower limbs, as proved by aortography. Sixty-one cases are reported. In thirty-one the occlusion was in the aorta; in nine, in both iliacs; in seventeen, one iliac; in fourteen, the external iliac. Sympathectomy and resection of the occluded segment are satisfactory only in a minority, and arterial or venous grafts should be considered.

108. Thyroid shunt and continuous murmur in the thyroid region can be observed in goitre without hyperthyroidism.

109. Anatomopathologic studies of seven cases of arterial obliteration of the limbs and with obliteration of the terminal aorta and gangrene in individuals of 25 to 50 prove that it is a systemic disease with a progressive hyperplasia of the intima and occasionally thrombosis at the level of the maximum obliteration at the proximal end, especially of the aorta and iliacs. Therefore, the thrombosis is an epiphenomenon and Leriche's syndrome is only a stage within a generalized disease of the aortic system.

HYPERTENSION

110. The retrospective examination of a patient proves that essential hypertension shows up early in life and that metabolic effects are demonstrable even before the blood pressure becomes elevated.

111. Hypertensive patients (241) were followed from 10 to 32 years after the onset of their disease. Ninety-two and five-tenths per cent had essential hypertensions and the remainder were due to pregnancy or kidney disease. The apparent time of initiation was usually between 40 and 49, women predominating 3 to 1. Fifty-one per cent corresponded to Palmer's Groups 1 and 2 while the rest were in classes 3 and 4 (with complications). In the latter group the higher pressures above 220 systolic and 140 diastolic were registered much more frequently, although great oscillations were common to both groups. The most frequent complications were: angina pectoris, 43 per cent; congestive failure, 39 per cent; coronary thrombosis, 10 per cent; bundle branch block, 10 per cent; second and third degree left ventricular strain, 36 per cent; auricular fibrillation, 11 per cent; cerebral vascular accidents, 11 per cent; fundus oculi Grades 3 and 4, 7 per cent. Renal insufficiency was apparent in only two instances. Fifty-eight per cent showed more than one complication. Seventeen per cent of the congestive failure patients were still living 10 to 21 years after the onset of the complication. Papillary edema disappeared in all but one of nine patients within a few weeks or months.

112. The marked aggressiveness of the disease in certain patients is the basis for a diagnosis of arterial hypertension in evolution, the principal features of which were described.

113. Unilateral renal disease, when it is the cause of hypertension, gives rise to an acute, severe, and accelerated clinical picture different in many respects from the habitual picture of essential hypertension or chronic bilateral renal disease. After nephrectomy twenty patients were apparently cured while in another twenty the blood pressures were still high.

114. Thirty-one years of experience in the management of hypertension patients with different diets, drugs, and operations lead the author to stress the great importance of emotional factors and their bearing on the treatment.

115. Parenteral Vitamin A in daily doses of 300,000 U. for ten days reduced the blood pressure, especially the systolic, and the symptoms in hypertensive patients of group two. These results would be due to an increase of the renal circulation and neutralization of epinephrine.

116. Thiocyanates work through the vagus nerve and their effect persists if the arteriolar mobility is preserved; the toxic symptoms may be controlled by atropine. At the initial stage the blood level attained should be 8 to 10 mg. per cent and afterwards between 3 and 8. Blood levels above 15 are dangerous and when 30 mg. are reached very serious accidents may occur. Thiocyanates exist normally in the blood and may play a role in the transmission of vagal stimulation through changes in permeability.

117. Veratrum viride improves headache, nervousness, and fatigue although a significant fall of blood pressure was only noticeable in 37 per cent of patients. It was well tolerated in 25 per cent while the rest had digestive symptoms, bradycardia, and dizziness.

118. Another paper stresses the usefulness of veratrum viride as a hypotensive drug.

119, 120. Oral protoveratine is feasible as a long-term treatment for symptomatic hypertension in daily doses ranging from 0.4 to 1.5 mg. This report is based on twenty-two patients over 6 and to 30 months; headaches especially were controlled; adverse symptoms such as nausea, vomiting, giddiness are noticed one-half to two hours after treatment. After intravenous injections renal function decreases in the first thirty minutes; there is a fall in cardiac output, stroke volume, and left ventricular index reducing the mechanical work of the left ventricle which would explain its beneficial effect in hypertensive patients with left ventricular failure. A decrease in pulmonary artery and pulmonary capillary pressure would increase this effect.

121. Hexamethonium bromide was given subcutaneously to fifty severe hypertensives over eight months in doses ranging from 10 to 50 mg., twice to four times daily. The fall in the blood pressure figures was in proportion with the dosage administered. Similar results were attained by oral treatment, the daily amount varying from 375 mg. to 2 Gm. daily.

122. Experience over ten months with hexamethonium in nine malignant hypertensive patients with doses ranging from 40 to 150 mg. daily is reported. In four there was symptomatic relief, improvement in vision, and disappearance of papilledema despite impaired renal function in three of them. The other five died, although they experienced temporary clinical improvement. Of eighty-eight patients treated previously, in only three papilledema disappeared spontaneously.

123. Dorsolumbar sympathectomy is indicated in malignant hypertension under the age of 40. Four cases are reported with symptomatic relief although the blood pressure figures returned to their previous level after a few years; one has been controlled for seven years.

124. Sympathectomy (ninth T. to second L.) would prove beneficial in the heart failure of hypertensive disease.

125. The clinical observation of individuals with a traumatic arteriovenous fistula compatible with normal activity for ten or twenty years suggests a new surgical treatment for hypertensive patients. The operation was performed on dogs at the middle third of the thigh; a marked fall in the blood pressure follows but this afterwards rises and an equilibrium is established eventually at a lower level than previously. A ligature is placed then on the iliac vein at the thigh to prevent the arterialization of the venous circuit and the overload. Left ventricular strain electrocardiographic curves improve remarkably.

RADIOLOGY

126. The value of roentgen-photography on small films is stressed as certain abnormal patterns usually coincide with cardiovascular disease such as enlargement of the left ventricle and the aortic arch while in this method a mitral configuration or an enlarged pulmonary arch very often are produced by a normal heart.

127. Angiocardiography alters the T wave and S-T segments in different leads. Therefore, cases must be carefully selected before submitting them to this method.

128. A new angiocardiographic procedure is described with direct radiography in two planes synchronously at a speed of ten pictures per second with a simultaneous electrocardiographic tracing.

129. Aortography by injection in the carotid artery was performed in normal individuals and patients with congenital heart disease, thoracic, or abdominal aortic aneurysm. There were no ill results, although one of the patients was 75 years old.

130, 131. Aortography by catheterization through the radial artery was used in twenty-five cases of aortic aneurysm of difficult diagnosis and in twelve instances of persistent ductus arteriosus.

132. Experimental work on the same subject was carried out on dogs with perfect visualization of the important aortic branches including the coronary arteries, although the left auricle and pulmonary veins were opacified only once. There was one sudden death during injection in the coronary artery. Coarctation of the aorta and Taussig-Blalock's anastomosis were easily demonstrated after six weeks of their production, but occlusion of the coronary arteries could not be visualized.

133. Venograms in patients with obstruction of the upper vena cava system demonstrated an important communication route between the innominate veins. In occlusion of the left one the circulation is established through the intracranial veins, and when the obstruction is on the right, through the cross-connecting vein of the anterior jugular vein.

ELECTROKYMOGRAPHY

134. Bedside tracings have been recorded immediately after and for several days in myocardial infarction. A zone of immobility frequently larger than is suggested by the electrocardiographic changes appears on the lower margin of the left ventricle and persists for several weeks.

135, 136. Electrokymograms have proved the most accurate method to differentiate aneurysm and paramediastinal tumors, in accordance with the diffuse expansive or transmitted movements of the abnormal structure. In pericardial effusion and constrictive pericarditis the decrease in the movements disappeared after clinical or surgical cure. In myocardial infarction paradoxical movements and paralysis could be found, and it may be in certain cases an aid in diagnosis.

In mitral insufficiency the usual finding was a pansystolic expansion at the level of the left auricle and the pulmonary veins, although similar tracings are registered in normal individuals but only at certain levels. Its value is not yet established in mitral stenosis. In aortic insufficiency the amplitude at the aortic knob is double that at the pulmonary artery, there is an early and extensive diastolic expansion of the ventricle and abnormal anticipation and prolongation of the ventricular expulsion. Aortic stenosis has no significant tracing. Tricuspid insufficiency shows positive high pansystolic waves at the level of the vena cava and the diaphragm. In two instances of tricuspid stenosis high presystolic waves were noticeable at the diaphragm, right auricle, and vena cava. Pulmonary insufficiency shows great amplitude at the pulmonary artery hilum and pulmonary bed and an abnormal anticipation of the right ventricular expulsion. In interauricular patency there is a similar picture without the last feature, and in persistent ductus arteriosus the picture is similar to that of aortic insufficiency.

137. An electrokymographic study of the middle arch in oblique positions confirms that the left auricular appendix forms the lower portion of the middle arch in more than 50 per cent of normal individuals and in a large percentage of mitral stenosis even when a simple roentgenogram would not demonstrate it.

CARDIOGRAPHY

138. The injection of one hundred normal human hearts following Schlessinger's technique proved the following venous circulation differing from the classical descriptions: (1) The major coronary originates at the middle third of the anterior wall, and the minor one, less important than we believed, at the right posterior auriculoventricular ridge. (2) The anterior cardiac veins are important vessels and empty independently into the right auricle. (3) The posterior interventricular vein starts at the lower third of the anterior wall. (4) An abnormal Thebesius valve coincides with an interauricular communication.

PNEUMOGRAPHY

139, 140. Pneumomediastinum may be obtained by retropneumoperitoneum following the technique described by Ruiz Rivas of Madrid. It is most useful when combined with tomography.

141, 142, 143. Another method of producing pneumopericardium and pneumomediastinum by suprasternal puncture is described; around 300 to 400 c.c. of air should be injected, divided between the pericardium and the mediastinum. Adhesions may be visualized in this manner as well as pericardial disease; the only contraindication is advanced heart failure. It may be used combined with tomography or angiocardiography.

ELECTROCARDIOGRAMS

144. Distortion is discussed as an index of accuracy in the electrocardiographic machines.

145. The so-called skin current should be really termed electrode current as it is due to physical inequalities in the contact of both electrodes and the solution which separates them from the skin.

146. There is no definite criteria to decide whether an incomplete bundle branch block is pathologic or simply produced in normal hearts by myocardial zones which are delayed in leaving their quiescent state. Deep inspiration, Valsalva's test, right lateral decubitus, and additional chest leads are useful only in the case of an extensive conduction alteration, as the electrocardiogram is not altered by the different maneuvers for less extensive conduction alterations. In normal individuals the previous tests changed the tracing to a normal one. Radiologically it was found that when the signs of block were present in V_1 they corresponded to the right auricle and when in V_2 to the pulmonary conus.

147, 148. In doubtful cases of right bundle branch block additional tracings at the level of the second right intercostal space and below the ensiform appendix may prove useful when the morphology of V_1 is not typical. Different degrees of bundle branch block are described.

149. The potentials of the left auricle may be registered by an electrode placed in the conus of the pulmonary artery or in the horizontal portion of its right branch. For simultaneous registration of both auricles left catheterization into the descending aorta (for left auricle) may be used combined with right catheterization. With this method the waves of flutter and fibrillation are higher when the electrode is in the right auricle than when it is in the descending aorta. Each wave of flutter or each fibrillation is a true auricular complex originated in centers of rapid auricular impulsion.

150, 151, 152. Human epicardial direct tracings are usually similar to the precordial ones on the left side, but there is no clear correlation on the right ventricle. In accord with the position and rotation of the heart and the extension of the epicardial surface in which late R waves are recorded rSr′ or rSR′ complexes are registered in normal precordial leads. Late R deflections are seen in high right precordial leads.

153. Intermittent and transitory bundle branch block which occur in conditions such as lengthening of diastole after premature beats, myocardial disease of infectious origin, toxic drugs, etc., are described. The fact of the repetition of the same pattern after several years and the favorable prognosis when there is no other change is noticed.

154. Noncomplicated hypertensive patients were classified in three groups as regards exercise tests: (1) with a normal electrocardiogram and showing S-T-T changes afterwards; (2) with a tall R in V_5, deep S in D_1, or a straight S-T segment in D_1, aV_L or V_5 in which the abnormalities in repolarization were increased; (3) with a typical S-T and T of left ventricular hypertrophy that changed towards normal after the effort. In the first group these changes would be an early sign of left ventricular hypertrophy.

155. In healed coronary thrombosis of at least three months standing with or without heart failure or angina pectoris, although the effort was reduced in most cases, there was a positive test alteration of the QRS voltage and of the electric axis coinciding with the change in the ventricular gradient; the former would be the cause of the ST-T changes. Drugs such as Aminophylline, Khellin, and Pentanitrine diminished the positivity of this test.

156. Digitalis in therapeutic doses (1.20 Gm. of powdered leaf over 3 days) produces in normal or almost normal electrocardiograms reversible changes in the following leads: in left ventricular hypertrophy and horizontal heart, D_1, aV_L and V_6; with vertical heart, D_2, D_3, aV_F and V_6; in right ventricular hypertrophy, D_2, D_3, aV_F, V_1, and V_2 and would also show up latent electrocardiographic ventricular hypertrophy. Alterations in repolarizations would be the cause. The same dosages of digitalis barely change the electrocardiogram of normal individuals.

157. Pregnancy alters P, Q, T, the electric position of the heart, the medium electric axis of QRS and T, and the ventricular gradient but does not give rise to arrhythmia or conduction disorders which would suggest cardiac involvement.

158. Electroshock and insulin shock therapy alter previously normal electrocardiograms giving rise to arrhythmia, changes of T and Q-T intervals, and at times alteration of QRS.

159. Carrion's disease or Peruvian wart in its anemic phase shows a tall sharp T connected with the increased potassium liberation due to red-cell hemolysis.

160. Infectious diseases alter practically all complexes of the electrocardiogram. Diphtheria can even cause death through myocarditis. Digitalis should not be used in this condition. In all other infectious diseases it may be used with care. Chagas' disease produces an inverted P and changes in the T. Rheumatic myocarditis must be appraised by its association with peri- and endocarditis.

161. The electrocardiogram proves useful in differentiating pericarditis of unknown origin, Hodgkin's disease, pericarditis and rheumatic pericarditis from tuberculous pericarditis. In the former the changes reverted to normal in a short period while in the latter the evolution is much more prolonged. Electric tracings in some cases of pleurisy, peritonitis, and tuberculous primary infection have led to the diagnosis of pericarditis without clinical or radiological symptoms. The electrocardiogram does not always return to normal after the reabsorption of the effusion, while in others the electric tracing was the only lead to the diagnosis of an old pericardial symphysis without circulatory repercussions and proved later at autopsy. After an operation the same phenomenon is ob-

served as some of the electrocardiographic abnormalities persist after the clinical cure. In elderly patients tuberculous pericarditis is rare, and constriction appears rapidly.

162, 163. A spatial polarity circle system is presented in a model, the frontal plane direction is determined from the limb lead polarities and the horizontal one from thoracic lead polarities, producing an arrow with a biaxial movement originating at the geometrical center of the model. Also the various instantaneous cardiac vectors can be projected on the frontal plane.

164, 165. Left bundle branch block and left ventricular hypertrophy are analyzed in connection with the spatial vectocardiogram. A cathode-ray oscillograph was used and the scalar deviations were compared with the corresponding vectorcardiogram.

166. The left ventricular hypertrophy signs in rheumatic aortic valvular disease appear with preference in precordial leads and V_F and rarely in the classical ones. When there are atheromatous or meso-aortic changes the heart is not verticalized as when the wall of the vessel is not diseased and the electrocardiographic signs appear in the standard leads and V_L. The verticalization of the heart with a healthy aortic wall would be produced by the systolic ventricular strain at the aortic arch.

167. The measurement of Q-T_c in acute rheumatic carditis would be the best single criterion for the evaluation of the efficacy of cortisone and ACTH in this condition. The rebound of Q-T_c after interruption of treatment foreshadows a recurrence of the rheumatic carditis, and its return to normal runs parallel with the clinical improvement.

168. Another paper stresses the advantages of the classification recommended by the Special Committee of the New York Heart Association for right bundle branch block and advises additional thoracic leads on the anterior wall of the right hemithorax in certain instances of incomplete bundle branch block.

169. The displacement to the left of the transitional zone in left bundle branch block could be due to the position of the heart, the right ventricular dilatation evidenced by a deep S up to V_6 or V_7 and at times acute cor pulmonale. In right bundle branch block the same displacement is almost always due to right ventricular dilatation and is seen in chronic cor pulmonale, mitral tricuspid lesions, auricular septal defect, Ebstein's disease, and septal infarct complicated with right bundle branch block.

170. The electrocardiographic interpretation should include: (1) rhythm, including frequency; (2) vectometry (electric axis, etc.); (3) interrelation of the electrogenetic manifestations and syndromes; (4) disease; (5) therapy. Instead of the numerical criteria in electrocardiograms, voltage is classed as high, low, or middle and the duration is either shortened, widened, or normal in the new electrocardiographic index suggested.

150, 151, 152, 171, 172, 173, 174, 175, 176. The changeable electric field of the heart is the basis of the new complementary and not supplementary leads which are termed discriminative of the classical leads and may prove very useful in pathology.

171. Complementary leads discriminative of the classical ones are based on Helmholtz's equation and are useful in doubtful cases when classical curves are normal.

174. For the study of the posterior and diaphragmatic zones of the heart, ample thoracic back leads can be taken in a craniocaudal direction; they are similar to esophageal leads.

175. Occasionally a lead back of the left leg is useful to establish the sagittal projection of the electric axis of P-T or QRS and assist in further exploration.

177. The auricular ventricular conduction in auricular fibrillation can be studied using the ventricular rate and the different R-R spaces in groups as an indirect index which can be altered by quinidine or digitalis; some nodal or idioventricular escapes correspond to almost complete auricular ventricular blockage.

178. Lead aV_R must be considered as a negative from the orientation current originated from all other dipoles in an infinitesimally short period of time and is similar occasionally to the left or right intracavitary ventricular potential and influenced at times by the changes in potential of the left and right ventricle.

179. An RSR pattern without conduction alterations in intraventricular conduction is common in right precordial leads, especially in the upper precordial zone when there is a sternal depression.

180. A U wave is almost constantly a normal finding in precordial leads; it reaches its maximum height in V_3 and is still positive in healthy individuals with a diphasic or inverted T in the right precordial leads. Its voltage is usually increased by exercise (75 per cent of cases), by digitalis, in normal individuals or hypertensive patients without heart involvement. In left ventricular strain there is an equal percentage of positive, negative, or isoelectric U waves. The inversion is more frequent in aortic insufficiency than in hypertension and also when digitalis is given in coronary thrombosis. When there is displacement of the RS-T segment we find a positive U in the corresponding precordial leads; afterwards it becomes inverted in conjunction with the T or disappears. In right bundle branch block it usually disappears in the right precordial leads while in left bundle branch block it is occasionally inverted. An inverted or diphasic U in left precordial leads can be an isolated abnormality in 1.33 per cent of cases; more than one-half of these were hypertensive persons.

181. The triortogonal vectorcardiographic system proposed by Duchosal gives the most accurate information as to electrophysiology of the heart. The main spatial axis of QRS and T was studied in fifteen normal individuals, and there was a marked concordance between the mean magnitude of both axes in opposition to what is common with other methods in which SA-T is usually larger than SA_{QRS}. The relation E.M.F. = 0.61, E reported by Wilson and confirmed by others proved that Einthoven's plane could not be considered as fully parallel to the surface of the body.

182. A method of spatial electrocardiographic exploration in three planes is described as follows: Frontal plane, D_3, aV_F, D_2,$-V_R$, D_1 and aV_L. Horizontal plane: Six leads similar to the usual precordial ones but placed at 30

degrees regular intervals from each other. Sagittal plane: Unipolar leads at 30-degree intervals at the positive ends of the axis corresponding to angles from 120 degrees to −30 degrees which would be denominated S_1 to S_6. S_5 would correspond to the anterior end of the horizontal anteroposterior axis.

183. A positive relationship between Q-T interval corrected according to Bazett's formula ($Q\text{-}T_c$) and the ventricular gradient (G) is determined and expressed in uA. A similar correlation was found with the deviations that the obtained (Go) ventricular gradient undergoes in relation to the corrected one (Go) following Ashman's tables, as Go deviations to the left are more frequent with the high $Q\text{-}T_c$ values while the deviations to the right are present with low $Q\text{-}T_c$ values.

184. Theoretically, Starling's law may be of no value in initial systolic strain but valid in increased diastolic heart filling. This view is based on clinical, radiologic, pathologic, and electrocardiographic data. A diastolic strain of the right ventricle shows an incomplete or complete right bundle branch block, while in a systolic strain there is a high R and a negative and symmetrical T in right chest leads. Diastolic strain of the left ventricle shows a high and late R wave followed by a positive tapering T in left chest leads, but if the strain is systolic there is a flattened or negative T (occasionally of the ischemic type) and a depressed S-T segment.

PAPERS SUMMARIZED

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97. Schlesinger, P., and Burlamaqui Benchimol, A.: The heart in Myxedema, Rio de Janeiro, Brazil.
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112. Taquini, A. C.: Evolutive Arterial Hypertension, Buenos Aires, Argentina.
113. Perera, G. A.: Clinical Characteristics of Hypertension Associated With Unilateral Renal Disease, New York, N. Y., U. S. A.
114. Ledbetter, P. V.: Thirty-one Years' Experience in the Management of Arterial Hypertension by an Internist, Houston, Texas.
115. Govea, J.: Treatment of Permanent Arterial Hypertension With Massive Doses of Synthetic Vitamin A by Intramuscular Via, Havana, Cuba.
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161. Coelho, E.: Electrocardiographic Changes in the Development of Tuberculous Pericarditis, Lisbon, Portugal.
162. Laranja, F. S., and Zao, Zang Z.: The "Spatial Polarity Circle System" for Obtaining Automatically the Spatial Direction of Any Cardiac Vector From Conventional ECG Leads' Polarities, Rio de Janeiro, Brazil.
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184. Cabrera C., E., and Monroy, J. R.: Systolic and Diastolic Strain of the Heart and Its Relation to the Electrocardiogram, Mexico, D. F.

Announcement

A SHORT CONTINUATION COURSE entitled ELECTROCARDIOGRAPHY with Dr. George E. Burch as Chairman will be presented through the Division of Graduate Medicine of Tulane University School of Medicine, New Orleans, La., between the dates of Nov. 30 and Dec. 9, 1953. The course will be limited entirely to electrocardiography. It will consist of a program designed primarily for beginners in the field and will include the study of electrocardiography and vectorcardiography. Considerable time will be devoted to the practice reading of tracings.

Book Review

SYMPATHETIC CONTROL OF HUMAN BLOOD VESSELS. H. Barcroft and H. J. C. Swan. London, 1953, Edward Arnold and Company, 165 pages.

While the history of research on nervous regulation of peripheral circulation goes back well into the past century, experimental information on human blood vessels is quite recent. The existence of important differences between species in the regulation of peripheral circulation has made systematic experimental work on human blood vessels mandatory as a basis for diagnosis and therapy, and much of this work has been performed by the authors.

The basic method used is volume plethysmography of the hand and forearm, a method which differentiates between the response of skin vessels (hand) and muscle vessels (arm). The responses of skin and muscle vessels differ in many experimental situations. For instance, Adrenalin constricts the skin vessels and dilates the muscle vessels, but there is also a secondary dilatory effect on the skin vessels, probably of central origin. The physiologic background of peripheral vascular regulation is intricate and requires a great deal of ingenuity in the attempt to analyze the various mechanisms involved. Experimental procedures used for this purpose include intra-arterial and intravenous infusion of adrenaline and noradrenaline, novocaine blockade of deep muscle nerves, "adrenic blockade," sympathectomy, direct and reflex response to heating and cooling, etc.

Some of the results are not surprising (for instance the quantitative demonstration of the effect of sustained and rhythmic contraction on muscle blood flow), but others are unexpected (for instance the apparent existence of two independent mechanisms regulating the circulation in muscle, the one dependent on metabolism, the other based on arteriovenous anastomoses controlled by the nervous system).

This critical review of a very fluid field of research is important and stimulating; many mechanisms have been sufficiently clarified, but it seems that even more problems are still open. The necessity for further research on one or the other specific question is emphasized in nearly every chapter.

Of particular clinical interest are the chapters on sympathetic denervation, on the action of adrenaline and noradrenaline on skin circulation and general circulation, on adrenergic blockade, on pheochromocytoma, and on the "vaso-vagal" syndrome (fainting). Although vasodilatation in muscle during fainting is well known, the details of the cause and mechanism of fainting are not clear. As the sympathetic nervous system mediates the vasodilatation in skeletal muscle and probably also in the splanchnic area and kidneys, there should be no vasodilatation or fall in blood pressure in totally sympathectomized subjects when they faint, but these persons are very prone to orthostatic faints. This is one example of the many paradoxes which need further exploration. It is of interest that the typical difference between the circulatory and metabolic effects of adrenaline and noradrenaline in small and moderate dosages tends to disappear with the massive output of these hormones in pheochromocytoma.

There is a condensed description of the technique of volume plethysmography in an appendix (p. 139 to 151); a simplified model for use in the ward is particularly interesting.

The book provides much factual information together with a critical discussion, but it is not really comprehensive and probably was not intended to be. For instance, the results of photoelectric plethysmography are largely ignored. Its merits are a solid, competent, and clear presentation of a very complex physiologic situation. It is the first number of a series of Monographs of the (British) Physiological Society. No better choice for the starting volume could have been made.

E. S.